Veterinary Ocular Pathology

a comparative review



Richard R. **Dubielzig** • Kerry L. **Ketring** • Gillian J. **McLellan** • Daniel M. **Albert**

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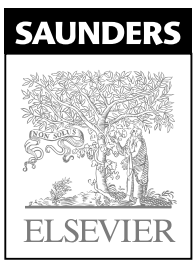
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Acknowledgements

It has been 30 years since Gustavo Aguirre asked me if I would be interested in reviewing ocular pathology cases for the benefit of the ophthalmology residents and faculty at the University of Pennsylvania, and 25 years since the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW) began receiving specimens. With more than 25 000 cases in the COPLOW archive and all these years of ocular pathology experience, I became motivated to put into a textbook what I have learned about veterinary eye pathology. I hope this will benefit those who are active in the field and those who will continue the work in the future.

I have found *Ocular Pathology* by Myron Yanoff and Ben Fine (Mosby) to be helpful in my own work and borrowed from their text the idea of combining clinical and pathology photographs. My goal is to present a more unified clinical and pathological context to understand veterinary ocular pathology. Like Yanoff and Fine, this book is in an outline format, because I have found that model helpful to access descriptive information.

One of the unique aspects of our text is that it uses the COPLOW database to provide information about the relative frequency of various diagnoses. Emphasis is given to conditions seen in the pathology laboratory. There is a bias toward removal of the globe and submission of the specimen, when ocular disease is seen as a risk to the health of the animal, such as cancer. For that reason, neoplastic conditions are over-represented in a pathology archive and, therefore, also in this ocular pathology text. When there is not a perceived risk to the health of the animal, there is little reason to remove an eye, unless it is both blind and painful or ugly. For this reason, we see severe intractable glaucoma, trauma, or inflammation over-represented in the pathology laboratory. We seldom see conditions that may cause visual impairment but leave the eye comfortable and unblemished. Retinal conditions, anomalies and treatable conditions are usually not submitted to the pathology laboratory and have received less emphasis in this book.

Readers should be aware that we present conditions that appear as diagnoses from the COPLOW laboratory but have not yet appeared in other veterinary literature. We hope that pathologists will use this text as a guide to diagnosis and that insight from the experience of someone who has managed a large caseload of ocular pathology will be valued. We expect that, in time, either the COPLOW laboratory or others will take the effort to properly document those topics that appear in the text but not in the peer-reviewed literature.

In ocular pathology, as in skin pathology, the clinician is able to make direct observation of the pathology both outside and inside the globe. That is why it is exciting to put together a text that is so rich in clinical photography. Kerry Ketring has been a careful recorder of the morphologic variants of ocular disease throughout his long and productive career. His photography skills are widely admired and he has assembled numerous photographic essays and atlases illustrating veterinary ophthalmology. It was a delight to work with Kerry on this project and his contributions add a rich dimension that bridges the gap between clinical ophthalmology and ocular pathology.

Although ocular pathology has been my main focus for three decades and, during that time, I have attended meetings of ophthalmologists, published in ophthalmology journals, and have daily dialogues about case material with ophthalmologists, my perspective is always as a pathologist. Co-author Gillian McLellan has made this text accessible to veterinary ophthalmologists. A veterinary ophthalmologist familiar with ocular pathology, she has an exceptional and comprehensive knowledge of the literature. Gillian is an academic veterinary ophthalmologist, with extensive experience in the practice of ophthalmology, who has used ocular pathology throughout her research career. Most importantly, she was able to rephrase my words and make them more appropriate and understandable to practitioners. Clinicians and pathologists use medical terminology in different ways and we see different case material. There are also different priorities and different goals in our approach to vision science. Gill's editing and reworking of the text has had a huge and positive impact on the final product. Dan Albert deserves to be acknowledged in many ways. He has been a friend, an inspiration, and a mentor for most of my career. Dan's sage advice was helpful in managing my career path. We are delighted that he agreed to read this material and write the 'Comparative Comments' interspersed throughout the text articulating the similarities and differences between veterinary ocular pathology and human ocular pathology.

The authors are also indebted to the support and skills of several individuals who made significant contributions to this project. Marsha Ketring was an invaluable resource, who put together the clinical photography for the text. Her skills with Photoshop and her ability to convert Kerry Ketring's images, which are archived as two-by-two slides, into high quality digital images, made this book possible. Doris Dubielzig's talents as an editor and wordsmith were also a valuable part of the project. She devoted a huge effort into taking the figure legends, written by two authors with different styles, and blending them so that the styles and word use are consistent. To compensate for a lack of familiarity with the technical language, she constantly sought the most accepted terminology. We are also indebted to Dan Williams, as well as Doris, who both entertained the McLellan-Williams twins while Gillian edited the book.

The soil from which this book has taken root has been the work of the Comparative Ocular Pathology Laboratory of Wisconsin

(COPLOW). The lab has received, photographed, processed, diagnosed and archived more than 3000 mail-in cases in each of the last 3 years. The results are maintained in a digital format that allows easy searching for case retrieval and quick comparative studies. This is the work of many individuals and they all deserve our appreciation. Kate Lieber, in particular, manages the nuts and bolts of the lab. She handles the billing, manages the money, supervises the student help and accommodates the needs of our frequent visitors. She has an amazing facility with the smallest details and makes order when all else slips towards chaos. Kate has great empathy for the clients and the animals, keeping us focused on the customer and not just the pathology. Dr Chuck Schobert is the coordinator of COPLOW's research projects. In addition to conducting his own research, he coordinates the projects of scientists at other institutions who use the collection for their studies. Chuck pioneers new immunohistochemistry techniques, interfaces with the electron microscopy laboratory, and interacts with veterinary students on both research and educational projects. To date, we have had 14 ocular pathology fellows study at and contribute to COPLOW. These young veterinarians, interested in careers in ophthalmology or pathology, have chosen to spend a year at COPLOW as a step toward reaching their career goals. These bright, motivated, energetic, and hardworking young people have forced me, daily, to explain, justify and clarify my thoughts about ocular pathology.

Richard R. Dubielzig, Madison, Wisconsin
2010

Introduction

The organ of vision, as it appears in the infinitely varied forms of animal life, has amazed and inspired man since prehistoric times. Observations regarding diseases of the eye across the animal kingdom can be found in the ancient writings of India, China, Assyria, Egypt, Greece, and Rome. From the time of Hippocrates, the study of the eye has brought together physicians and veterinary specialists in an attempt to understand ocular disease. Although not formally recorded in studies on medical history, the beginning of ophthalmology was also the beginning of comparative ophthalmology. As medicine and veterinary medicine evolved, the significant findings of the postmortem examination, including an examination of the eye, became important for understanding diseases. A notable example is Leonardo da Vinci's many dissections of both human and animal cadavers. Numerous early works in veterinary ophthalmology focused on the study of the equine eye. As early as the 13th century, Giordano Ruffo wrote a chapter on equine eye diseases in his text, *Ippiatrics,* and Theodorico Borgognoni mentioned equine eye diseases in the text, *Ippiatraia Mulomedicinae*. The continuing interest in the equine eye is evidenced in the 1600s, by the chapter on the eye in the book by Andrew Snape, *The Anatomy of the Horse*.

The founder of ophthalmic pathology is generally regarded to be James Wardrup (1782–1869), a Scottish general surgeon with a lifelong interest in the diseases of the eye of both man and horse. Subsequently, human and veterinary ophthalmic pathology specialties have for the most part evolved separately, except for the notable study of laboratory animals and experimental models. We hope this book will help to bring these separated disciplines together again as comparative ophthalmic pathology.

The early history of comparative ophthalmic pathology has been primarily the domain of veterinary ophthalmology, and its achievements have been well documented in review articles by Milton Wyman, a veterinary ophthalmologist, and Leon Saunders, a veterinary pathologist. The 19th century saw veterinary ophthalmology advance and the importance of veterinary ocular pathology gain recognition. J. Carver, a veterinary surgeon, published a significant study related to the pathology of the horse's eye and, with other publications on the eye of animals starting to appear, veterinary ophthalmology developed as a viable discipline in European veterinary schools. Urbain Leblanc, a Parisian veterinarian, wrote a book on veterinary ophthalmology that was later translated into German. With Helmholtz's discovery of the ophthalmoscope in 1850, the ability to diagnose ocular disease in humans and animals became a reality.

The late 19th through the early 20th century was a critical period for veterinary ophthalmology, with increased activity in veterinary schools in Europe. In Berlin, Heinrich Möller, a veterinarian, made major contributions to veterinary ophthalmology, which were included in his book, *Lehrbuch der Augenheilkunde für Tierärzte*. Physicians teaching ophthalmology at the veterinary colleges developed a broad interest in ocular diseases in animals, and some, like Rudolf Berlin at the Veterinary College of Stuttgart, became interested in pathology. Josef Bayer, an Austrian physician and veterinarian, was devoted to the study of equine recurrent uveitis; while at the Vienna Veterinary College, he examined hundreds of enucleated eyes of horses. His findings were published in books and papers, and many of the specimens ended up in a notable museum collection in Vienna.

By the late 19th and early 20th century, the study of veterinary ophthalmology and veterinary ocular pathology was well underway throughout Europe. In Vienna, Otto Überreiter made important observations on canine glaucoma and equine cataract. In Hungary, veterinary ophthalmology was a topic of research and teaching at the Royal Veterinary College. Béla Plósz worked on the ocular histology of farm animals and studied lenticular opacities of horses. László Szutter was active in the area of ocular pathology and wrote a book, *Tierärztliche Augenheilkunde*. In England, Edward Nettleship, an ophthalmic pathologist at Moorfields Eye Hospital in London, published information on ocular diseases in dogs as well as humans, and George Coats, also an ophthalmic pathologist at that institution, studied congenital anomalies of animals' eyes. Edward Hilding Magnusson, a veterinary pathologist, described observations of hereditary retinal atrophy in the Gordon setter, and Theodor Kitt, a pathologist, produced the first textbook of veterinary pathology to seriously treat the subject of ophthalmic diseases (*Lehrbuch der pathologischen Anatomie der Haustiere*). Henry Gray, an English veterinarian, contributed to the literature on veterinary ophthalmology, while in France, Eugéne Nicolas, a veterinary ophthalmologist, published a text on veterinary and comparative ophthalmology (*Ophtalmologie, Vétérinaire et Comparée*). Nicolas' book was translated into English by Henry Gray and served as a major source of information for veterinarians in the British Empire and in the United States into the 1950s.

The 5th and final edition of Kitt's textbook appeared in 1927, and three decades elapsed before a comparable section on the diseases of the eye was published. This occurred in the American textbook on veterinary pathology published by Thomas C. Jones. Jones had previously published a series of articles on ocular pathology, particularly on uveitis in horses. Then, in the early 1950s, another veterinary pathologist in the United States, Leon Saunders, published a paper in the *Cornell Veterinarian* on blindness in dogs and a paper in the *Journal of Comparative Pathology* on intraocular lesions of canine distemper. In 1957, Hilton A. Smith and Thomas C. Jones included a chapter on ocular pathology in their textbook, *Veterinary Pathology*. This book

chapter marked the beginning of renewed interest in veterinary ophthalmic pathology, especially in North America, and included information on intraocular tumors in dogs by veterinary pathologists Leon Saunders and Charles Barron.

During the 1960s, veterinary ophthalmology and veterinary ocular pathology continued to evolve in the United States. In 1964, William G. Magrane started a clinical practice focused exclusively on veterinary ophthalmology, and Stuart Young, a veterinary pathologist at Colorado State University and honorary diplomate of the American College of Veterinary Ophthalmologists (ACVO), began to be actively involved in veterinary ocular pathology. In 1968, the main topic of the annual meeting of the American College of Veterinary Pathologists (ACVP) was ophthalmic pathology, with Lorenz E Zimmerman, head of the Ophthalmic Pathology Branch of the Armed Forces Institute of Pathology (AFIP), as the featured guest.

The development of veterinary ophthalmology and veterinary ocular pathology continued in the United States during the 1970s. In 1974, Lionel Rubin, a veterinary ophthalmologist, published an atlas of veterinary ophthalmoscopy that included information on both domestic animals and laboratory animals. Included in the textbook were pictures, provided by Leon Saunders, of histopathologic findings in the retina that correlated to the funduscopic pictures. This was the beginning of many subsequent interactions between clinical veterinary ophthalmologists and veterinary ocular pathologists. William Carlton, a veterinary pathologist at Purdue University, routinely examined enucleated eyes as part of a diagnostic service and incorporated his findings into material for a graduate course on ophthalmic pathology. At this time, Leon Saunders was rewarded for his contribution to veterinary ophthalmology by becoming an honorary diplomate of the ACVO, and another veterinary pathologist, Richard Dubielzig, began to give lectures on comparative ophthalmic pathology.

During the 1980s, the findings in diagnostic veterinary ophthalmic pathology from previous years of study were being shared and organized. The C L Davis Foundation offered symposia on ophthalmic pathology. Brian Wilcock from the University of Guelph, Richard Dubielzig, and William Carlton were invited speakers. In December 1980, a symposium on comparative ophthalmic pathology was held in Chapel Hill, bringing together veterinary ophthalmologists and pathologists with an interest in comparative ocular pathology. This symposium was organized by two veterinary ophthalmologists actively involved in comparative ocular pathology: Robert Peiffer Jr, at the University of North Carolina, and Robert Trucksa, at the AFIP. Among the presenters was Richard Dubielzig. The symposium was followed by the publication of the textbook, *Comparative Ophthalmic Pathology*, in 1983. This textbook contained contributions from veterinary pathologists William Carlton, Brian Wilcock, and Jantine van der Linde-Sipman from the University of Utrecht; and veterinary ophthalmologists Stephen Bistner from the University of Minnesota, Craig Fischer from the Animal Eye and Medical Clinic of Tampa Bay, Charles Martin of the University of Georgia, Ron Riis of Cornell University, and Frans Stades of the University of Utrecht.

This symposium gave rise to the ophthalmic pathology short course, 'The Histologic Basis of Ocular Disease', which included Robert Peiffer, Brian Wilcock, Richard Dubielzig, William Carlton, Leon Saunders, Herb Whiteley, and Stuart Young as faculty members. The faculty gradually changed over the years to include additional veterinary pathologists and ophthalmologists with an interest in veterinary ophthalmic pathology. The course continues to meet every other year and has been integrated into a larger course on veterinary ophthalmology sponsored by the ACVO (*William Magrane Basic Science Course in Veterinary and Comparative Ophthalmology*).

In the 1990s, the International Life Sciences Institute (ILSI) sponsored a course, organized by Thomas C. Jones of the Harvard Medical School, Ulrich Mohr of the Hannover Medical School in Germany and Yoichi Konishi of the Nara Medical University on the pathology of the eye that was offered in the three countries. During this period, ILSI sponsored a book by Thomas C. Jones, Ulrich Mohr, and Ronald D. Hunt, entitled *Eye and Ear*, which discussed the pathology of the eye and ear in laboratory animals. Although the book was not a comprehensive review, it mentioned comparisons with other species and with similar lesions in man. Also at this time, the topic of veterinary ocular pathology was presented at the annual meeting of the ACVP. This meeting was held jointly with the annual meeting of the ACVO to foster the interactions between veterinary pathologists and veterinary ophthalmologists.

In the present millennium, Brian Wilcock and Richard Dubielzig were honored for their advancements in the area of veterinary ophthalmic pathology by becoming honorary diplomats of the ACVO. In addition, Kenneth Simons, an ophthalmologist with expertise in ocular pathology from the Medical College of Wisconsin, and Robert Peiffer, edited a publication entitled, *Ocular Tumors in Animals and Humans*. This publication took the novel approach of combining information on veterinary and human ocular oncology for comparative purposes. The editors solicited contributions from experts in human ocular pathology (Daniel Albert from the University of Wisconsin); veterinary ocular pathology (Jeffrey Everitt, CIIT Centers for Health Research, and William Carlton); and veterinary ophthalmology (Nedim Buyukmihci from the University of California in Davis, Bernard Clerc from d'Afort Veterinary School, Craig Fischer from Animal Eye Clinics of Florida, Gia Klauss from the University of Wisconsin, Denise Lindley from Animal Eye Consultants, John Mould from the Glasgow University Medical School, and Claudio Peruccio from the University of Turin).

The present book, *Veterinary Ocular Pathology: a Comparative Review,* is an accumulation of years of painstaking observations regarding the gross and microscopic appearance of eyes from a wide variety of species with naturally occurring and experimentally induced disease. The book draws heavily from the extensive collection of ocular pathology specimens housed at the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW). With the same spirit of enthusiasm and interest in discovery as their predecessors in the field, Richard Dubielzig and his associates have written a textbook on comparative ophthalmic pathology that is current and comprehensive, to aid ophthalmologists and pathologists in both the veterinary and human medical fields.

Daniel M. Albert
James A. Render
2010

Chapter 1

The principles and practice of ocular pathology

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OBJECTIVES

- To characterize the case material seen in an ocular pathology service
- To present the basics of tissue handling
- To present the nuts and bolts of an ocular pathology service.

GENERAL POINTS

Throughout this book, when relevant, the collection of the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW) will be referenced to provide data regarding the relative numbers for categories of disease. The COPLOW collection as it exists at January 2008 will be used. Throughout the book, at the conclusion of each chapter, readers seeking further detail will find lists of suggested published texts, papers and other source material. It should be noted that these lists are intended to be illustrative, rather than exhaustive.

Comparative Comments

Most human ocular pathology laboratories handle all of the tissue removed by ophthalmologists. In addition to globes, there are exenteration specimens, including the lids and orbital contents, or the contents of the globe after evisceration surgery. The majority of specimens, however, are skin lesions, conjunctival lesions, and orbital lesions following incisional or excisional biopsy.

Characteristics of eyes submitted to the COPLOW pathology service

Reasons for submissions: Most submissions are from animals where the globes have been enucleated in the interest of the patient with the following justifications:

- Blind, non-cosmetic and painful eyes
- To facilitate the diagnosis of a systemic disease, e.g. blastomycosis
- To remove a mass lesion perceived to represent a threat to the general health of the animal, should local invasion or metastatic disease subsequently occur.

Species represented include:

- 68% canine (15 016 cases)
- 24% feline (5203 cases)
- 4% equine (758 cases)
- 4% other (1.2% avian).

Tissue:

- Enucleated globes: 67%
- Evisceration specimens: 10%
- Other specimens: 23%

Disease type (these categories are not mutually exclusive):

- Neoplasia: 39%
- Glaucoma: 34%
- Inflammation: 29%
- Trauma: 15%
- Congenital disease: 2%.

Characteristics of conditions infrequently encountered in the pathology laboratory

Conditions that have largely cosmetic implications:

- Breed-related pigmentary variations
- Congenital abnormalities where vision and comfort are not impacted and which remain static
- Non-progressive focal lesions, e.g. corneal scars.

Conditions that may be successfully treated by means other than enucleation or excision including:

- Inflammatory conditions amenable to medical therapy, e.g. chronic superficial keratitis (Fig. 1.1)



Figure 1.1 Canine chronic superficial keratitis (degenerative pannus). This potentially blinding disease is seen frequently, but treated successfully with anti-inflammatory topical medications and seldom results in a pathology submission. German Shepherd dog, 5 years old: the right cornea illustrates temporal pigment with a cellular infiltrate and neovascularization extending nasally.

- Cataract: cataracts are generally removed surgically by phaco-emulsification and specimens are seldom submitted for histopathology

Conditions that may affect vision but rarely necessitate eye removal, such as:

- Retinal degenerations, including progressive retinal atrophy (Fig. 1.2)
- Chronic but inactive keratitis
- Optic neuritis or compression without progressive disease.

Comparative Comments

A large percentage of the globes removed and submitted to a human ocular pathology laboratory is composed of blind eyes following surgical or non-surgical trauma. Others represent end-stage diabetes, glaucoma, vascular occlusion, retinopathy of prematurity, phakomatoses, and malignant tumors. Criteria for enucleation are similar in that, except in the case of neoplasia, only blind eyes that are painful and/or disfiguring are generally removed.

COPLOW RECOMMENDED TISSUE HANDLING PROCEDURES (Figs 1.3, 1.4)

Enucleated globes

- Immediately dissect all extraneous tissues from the globe, unless directly involved in the pathologic process or considered important for orientation, e.g. conjunctival squamous cell carcinoma or an orbital meningioma
- Identify the location of the lesion of interest with a suture or a mark or provide a simple drawing.

Adnexa and other soft tissues

- Label each tissue submitted using sutures or ink to provide the pathologist with anatomic orientation. A simple drawing is also often an important aid in orientation

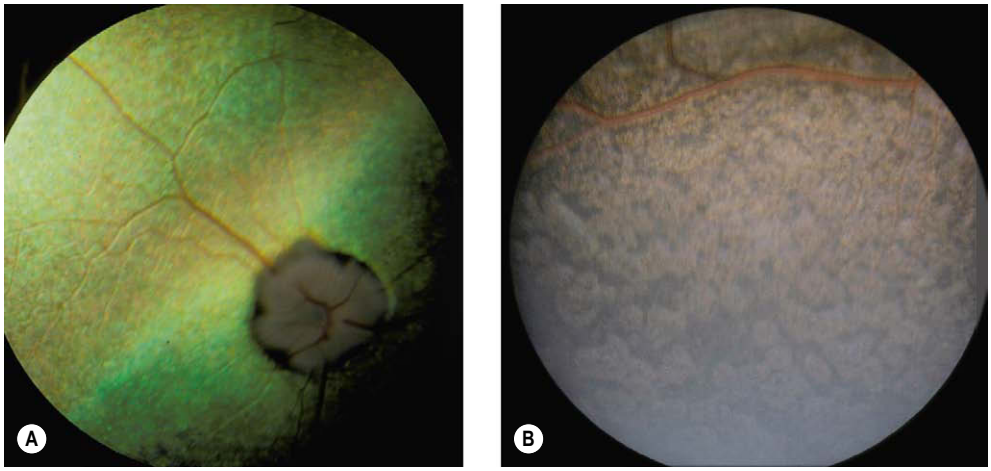


Figure 1.2 Progressive retinal atrophy (PRA). Funduscopic images of two cases of canine progressive retinal atrophy. There is no advantage to removing the eye from an affected dog. The pathologist is occasionally asked to verify that there is retinal atrophy when the eye is removed for other reasons or in globes removed at necropsy. By this time, the atrophy might be end-stage, when the best diagnosis is that the atrophy may or may not be compatible with PRA. (A) Akita, 2.5 years old: photographed with a neutral density filter, the tapetum is hyperreflective, retinal vessels are attenuated, and the optic disc is pale. (B) Labrador Retriever, 3 years old: the non-tapetal retina has a cobblestone appearance caused by depigmentation and pigment clumping of the retinal pigment epithelium (RPE).

- Tiny fragments of tissue that cannot be properly oriented should be identified as to their anatomic origin or source. If they are all from one source, they can be processed and sectioned together but, if they are each from different areas, they might have to be labeled separately
- Tissues prone to wrinkling or folding, like keratectomy specimens, should be supported on plastic, not paper or wood (Fig 1.4)
  - Avoid placing delicate tissues onto porous material, like wood or paper because they will adhere to these materials and may be destroyed during attempts to remove them from these substrates (Fig. 1.5).

Bone

- The pathologist should be alerted to the presence of bone in a sample in order to ensure that the tissue is decalcified prior to further processing and histo-sectioning
- A simple drawing on the submission form will help with the orientation of a specimen with a bony component.

Tissue fixation and mailing

General considerations in the selection of fixatives for the eye (Table 1.1)

Regardless of the fixative used, the volume of tissue to be fixed should be kept to a minimum, without sacrificing the integrity of the tissue's anatomic orientation.

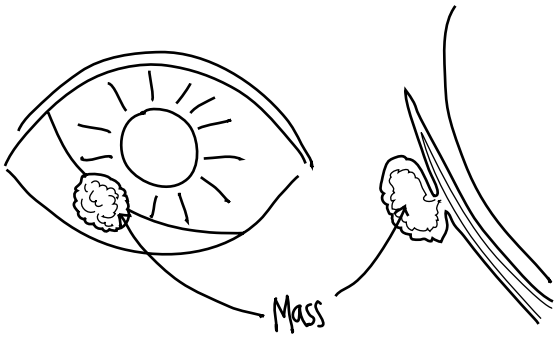


Figure 1.3 A drawing by the submitting clinician can be very useful in understanding the orientation and anatomic distribution of a lesion.

Formalin (10% neutral buffered formalin, or 4% formaldehyde)

- 100% formalin is a concentrated solution (40% w/w) of formaldehyde in water.
- This most common of fixatives is cheap and effective as a general all-purpose fixative.

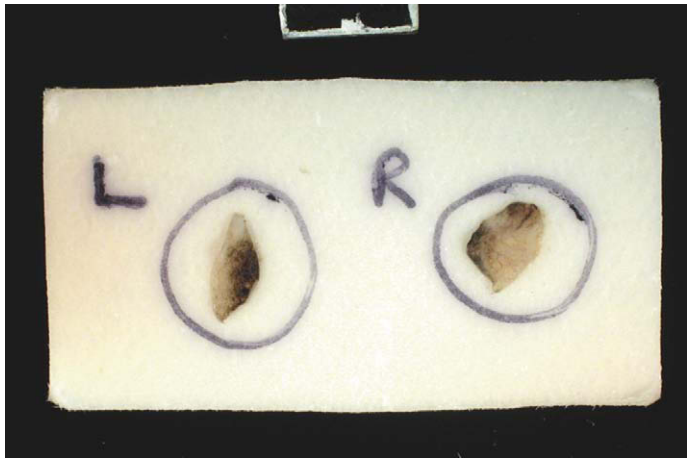


Figure 1.4 Keratectomy specimens mounted flat on plastic. These specimens from the left and right eyes are mounted on a non-absorbent surface, which will allow them to fix flat and rigid and make orientation easier.



Figure 1.5 Evisceration sample on paper. This specimen was wrapped in absorbent paper, which is difficult to remove without damaging the tissues.

Table 1.1 Comparison of fixatives for ocular tissues

FIXATIVE	CONTENTS	ADVANTAGES	DISADVANTAGES
Formalin	Formaldehyde	Cheap, fast, good general fixative	No serious disadvantages
Glutaraldehyde	Glutaraldehyde	Best for electron microscopy	Slow penetration. Must open the globe for surface fixation
Davidson's	Formaldehyde, ethanol, acetic acid	Added rigidity, excellent retinal fixation	Shrinkage, not as good as formalin for EM
Bouin's	Picric acid, formaldehyde, acetic acid	Added rigidity plus good for immunohistochemistry	EM impossible, opaque yellow color, dry picric acid is explosive

- Favorable qualities of formalin fixation:
  - Inexpensive
  - Excellent tissue penetration
  - Very good tissue fixation
  - Very good preservation of gross anatomic pathologic detail for photography and for selection of site for further processing
  - Adequate but not ideal for both electron microscopy and immunohistochemistry
- Unfavorable qualities of formalin fixation
  - Less than adequate tissue rigidity can lead to folding artifacts and artifactual retinal detachments.

Bouin's fixative (picric acid, formaldehyde, and glacial acetic acid)

Favorable qualities of Bouin's fixative:

- Excellent tissue rigidity making it easy to maintain the shape of the globe and prevent artifactual retinal detachment
- Excellent quality of retinal preservation in paraffin sections
- Excellent for immunohistochemistry.

Unfavorable qualities of Bouin's fixative:

- Requires prompt, timed changes into aqueous washes and subsequent preservation in alcohol
- Imparts an opaque yellow color to the fixed tissues which distorts the appearance for photography or site selection
- Tissue penetration is inferior to that of formalin, Bouin's should therefore be avoided when it is necessary to fix the globe and surrounding tissues without separating them
- Inappropriate for electron microscopy
- Picric acid is dangerous, becoming explosive when it dries. It is, therefore, tightly regulated from a mailing perspective.

Davidson's fixative (formaldehyde, alcohol, and glacial acetic acid)

Favorable qualities of Davidson's fixative:

- Excellent tissue rigidity making it easy to maintain the shape of the globe and to prevent artifactual retinal detachment
- Excellent tissue penetration
- Excellent quality of retinal preservation in paraffin sections
- Excellent for immunohistochemistry.

Unfavorable qualities of Davidson's fixative:

- Requires timed changes into aqueous washes and preservation in alcohol
- Imparts a white opacity to the tissues, which is not as unfavorable as the yellow color of Bouin's but still distorts tissue appearance and interferes with photography
- Inappropriate for electron microscopy.

Glutaraldehyde (often combined with purified formaldehyde or paraformaldehyde to increase tissue penetration)

Favorable qualities of glutaraldehyde fixative:

- The best fixative for electron microscopy
- Imparts tissue rigidity
- Excellent preservation of true tissue colors for photography.

Unfavorable qualities of glutaraldehyde fixative:

- Must be saved frozen or it deteriorates with time
- Glutaraldehyde is very caustic if it comes in contact with unprotected skin



Figure 1.6 Formalin leakage in mailing. Damage to a submission form inadequately protected from fixative leakage (arrow).

- Must be changed into buffer solution
- Very poor tissue penetration so that only thin or carefully trimmed tissues will fix adequately
- Poor for immunohistochemistry
- Less suitable for use with paraffin embedding, glutaraldehyde is often used in conjunction with plastic sectioning techniques.

General considerations in the mailing of specimens

General considerations

- It is the responsibility of the individual submitting a specimen to ensure that they are familiar with the rules and regulations regarding the mailing of medical specimens and fixative chemicals. These regulations vary depending on the geographic location, the service used, and the fixatives used
- Under some circumstances, the regulations pertaining to formalin in the mail do not apply provided the dilution is less than 10%.

Packaging

- The volume and concentration of fixative can be reduced for mailing once fixation has been accomplished
- Never squeeze unfixed tissue through a narrow topped container, as the fixed tissue will be difficult to retrieve from the container
- The wet tissue must be carefully protected in an unbreakable rigid container and in a waterproof wrapping. The paperwork should be separately wrapped and waterproofed (Fig. 1.6)
- The container should be mailed in a second crush-proof container.

Comparative Comments

The basic principles of tissue handling and fixation are similar for human ocular tissues, although formaldehyde is the fixative of choice. In many laboratories, eye bank eyes, either unused or following removal of the cornea, are examined.

Trimming and photography

Techniques for trimming globe for processing

Plane of section

- The default plane of section for species with a tapetum is the vertical section which samples the tapetal (typically superior) and non-tapetal (typically inferior) retina
- Exceptions are made to sample lesions in the temporal or nasal aspect of the globe
- The horizontal plane is preferred in primates because the fovea is temporal to the optic nerve
- The horizontal plane is also useful for avian globes because it is easier to obtain a section which samples the optic nerve and pecten along with the lens and pupil
- In rodents with extremely small eyes, trimming is to be avoided and the whole globe is submitted and oriented at the time of paraffin embedding.

Select a standard technique for trimming globes. Generally, the goal is to obtain a histological section that includes the optic nerve and passes through the pupil. Below are several techniques that are helpful:

1. Make the initial cut near the optic nerve. The lens is sectioned with a quick forceful cut while supporting the globe on the cutting board. This is the preferred technique in COPLOW (Fig. 1.7)
   - A major advantage of this technique is that sections may be obtained after only a few step sections from the embedded tissue to reach the optic nerve
   - Another advantage is that the globe is cut close to the anatomic center, which is appealing for the purpose of photography
   - The disadvantage is that the lens is often misplaced or damaged during trimming.
2. Make an initial cut which avoids the lens, with subsequent step-sectioning the tissue in paraffin to achieve a central cut
   - An advantage of this technique is that the lens is untouched and less likely to be artifactually dislodged
   - Disadvantages are that the off-center cut is not ideal for photography and the sectioning process is time-consuming and expensive.
3. Ensure the inclusion of lesions in the section plane
   - The ideal is to have the clinician indicate the location of a focal lesion in the globe with a careful description and drawings, as well as some indication directly on the tissue with a suture or another marking technique
   - Gentle palpation of the globe is valuable in detecting large localized lesions before sectioning. The orientation of the initial section can be changed in such a way as to sample the palpable lesion
   - 'Candling' the globe with a bright light in a darkened room can help to localize an opaque focal lesion
   - Careful examination of the sectioned globe using a dissecting microscope facilitates the identification of focal lesions. Additional steps may then be indicated to sample a focal lesion as indicated below
     - Re-cutting of the primary calotte so that only the segment of the globe with the lesion is embedded
     - Instructing the histology technician to step-section to a specified depth to sample focal lesions.

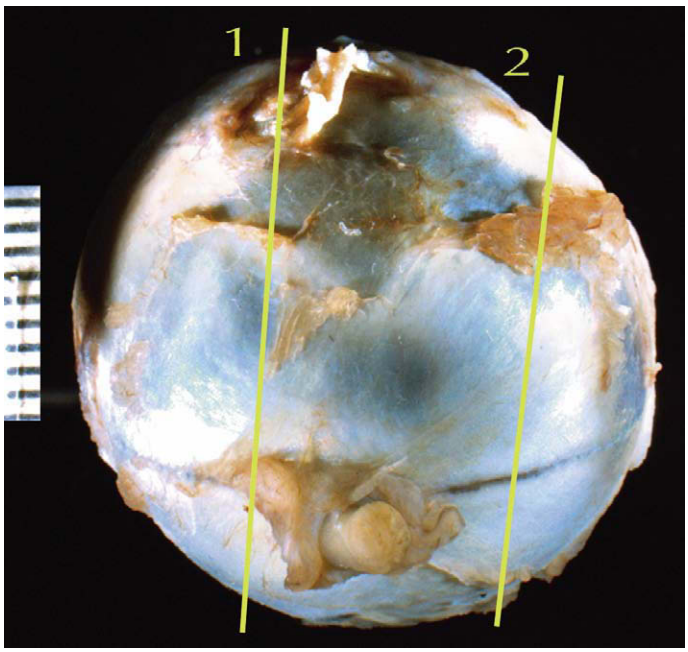


Figure 1.7 Landmarks for trimming with an initial central cut. A canine globe is oriented to reveal the landmarks for proper trimming in the vertical plane. The first cut is made at plane 1 and the second cut is made at plane 2.

Comparative Comments

Trimming and photography are carried out in a similar manner in veterinary and human ocular laboratories. Likewise, special stains are similarly employed.

SPECIAL STAINS AND OTHER HISTOLOGICAL TECHNIQUES COMMONLY USED IN OCULAR PATHOLOGY

Alcian blue-PAS (Fig. 1.8)

This is a very useful stain for the globe because the PAS stains carbohydrate rich proteins such as basement membranes, including lens capsule and Descemet's membrane, and zonular ligaments. The Alcian blue stains the hyaluronic acid of the vitreous.

Trichrome stain (Fig. 1.9)

The various trichrome stains are mainly useful to distinguish collagen from other protein deposits and to recognize cellular cytoplasm, as in muscle cells.

Melanin bleach (Fig. 1.10)

Various techniques are used to bleach the melanin pigment in tissues, allowing the observer to visualize features of tissue differentiation and nuclear details.

Polarized light (Fig. 1.11)

Examination of the tissues using intense polarized light will highlight tissue deposits with a repeating molecular structure such as collagen,

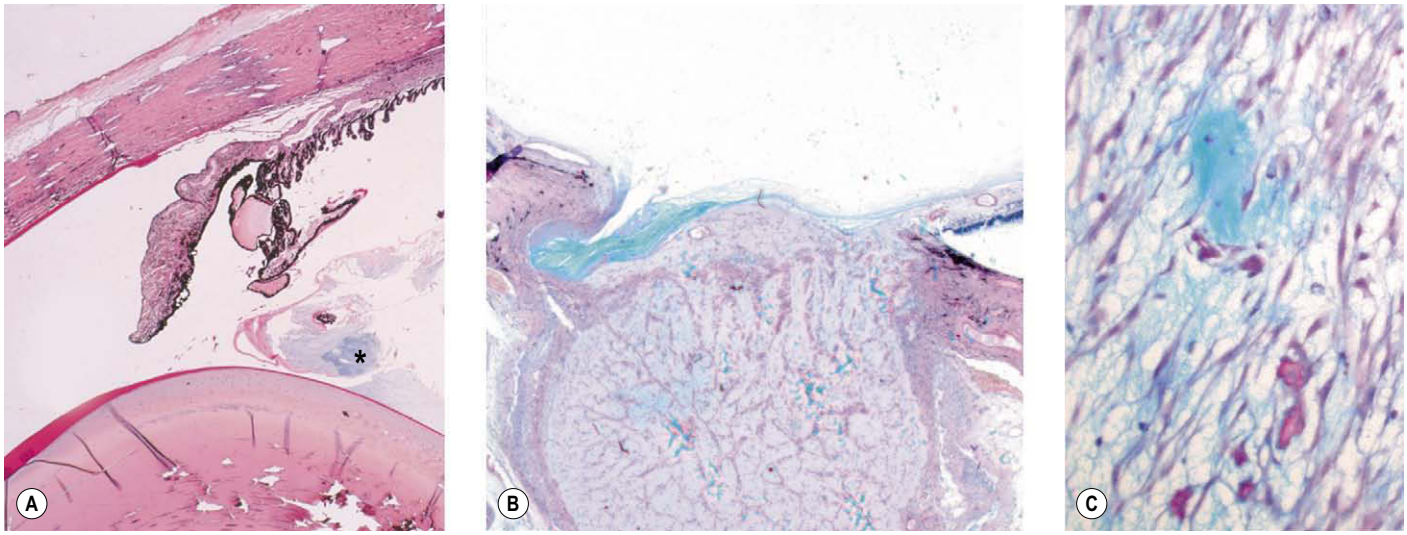


Figure 1.8 Alcian blue stain. (A) A subgross photomicrograph of a feline globe showing Alcian blue staining of the anterior vitreous face (*). (B) Low magnification photomicrograph of feline glaucoma showing Alcian blue-stained vitreous material pushed into the optic nerve head in Schnabel's cavernous atrophy. (C) Photomicrograph showing myxosarcoma with characteristic Alcian blue-stained mucoid material in the intercellular spaces.

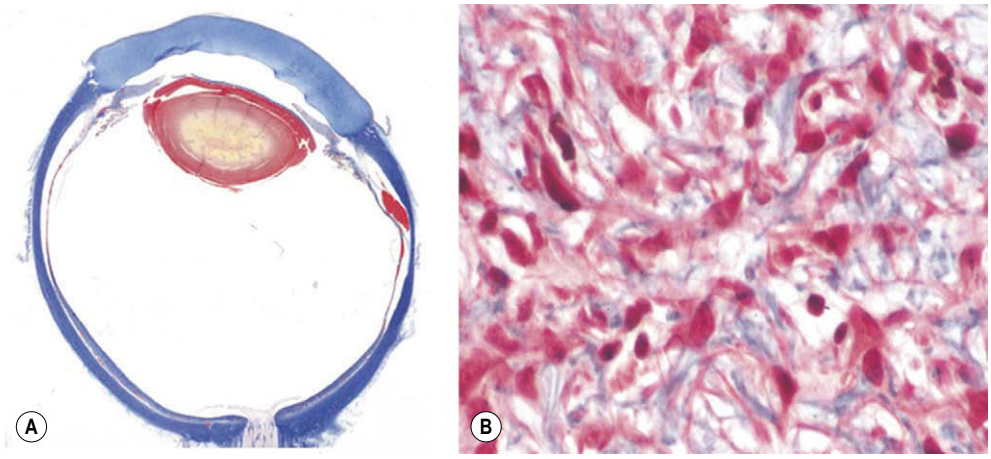


Figure 1.9 Trichrome stain for collagen. (A) Subgross photomicrograph of a trichrome-stained normal globe from a tapir showing the collagen of the sclera and cornea. (B) Photomicrograph showing the cellular and collagen matrix typical of a spindle cell tumor of blue-eyed dogs. The delicate trichrome-positive collagen matrix appears in blue.

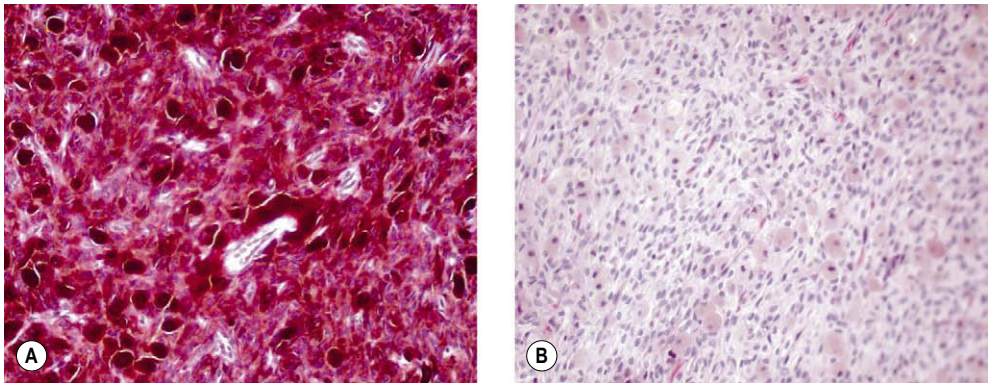


Figure 1.10 Melanin bleaching. (A) A non-bleached uveal melanocytoma in a dog. (B) The same tumor after bleaching the melanin pigment.

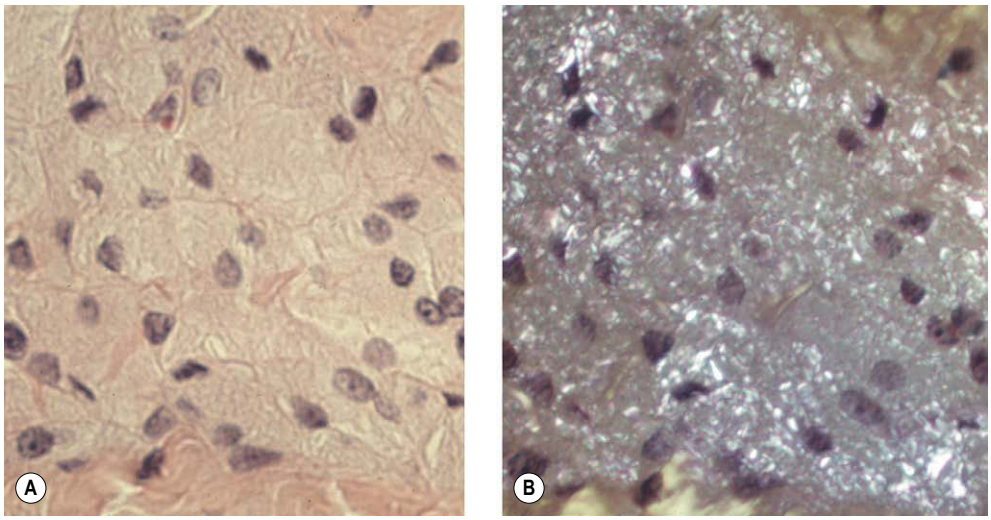


Figure 1.11 Birefringence with polarized light. (A) Phagocytic cells within a lipogranuloma adjacent to a canine meibomian gland tumor (H&E). (B) The same field viewed with polarized light showing the birefringent nature of the cytoplasmic inclusions.

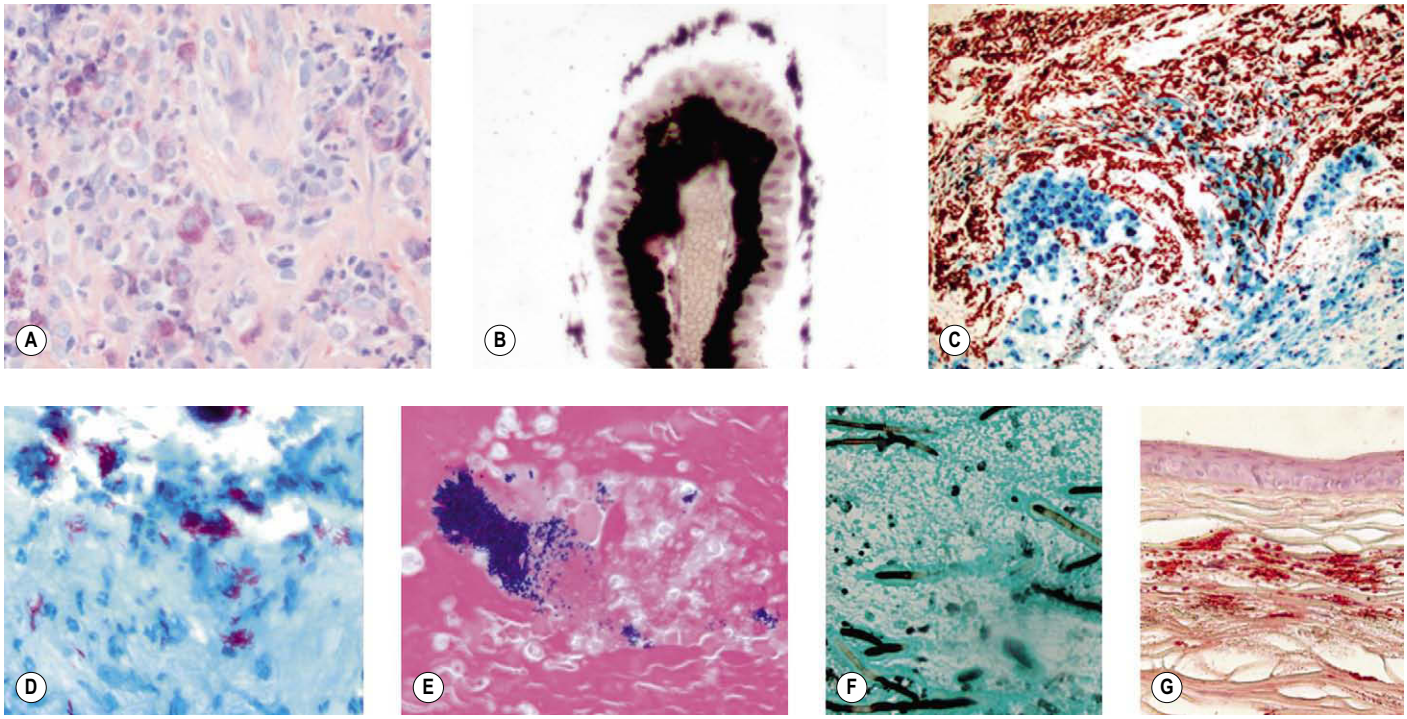


Figure 1.12 Other special stains. (A) Photomicrograph illustrating mast cells stained with toluidine blue. (B) Photomicrograph of the pars plicata of a dog showing elastin-positive staining of zonular ligaments with Verhoeff's van Gieson stain. (C) Hemosiderophage cells in the iridocorneal angle of a dog stained with Prussian blue. (D) Acid-fast positive bacilli stained with Ziehl–Neelsen stain. (E) Mineralized material in a cataract stained with the von Kossa stain. (F) Fungal hyphal elements stained with Gomori's methenamine silver stain. (G) Corneal stromal lipid stained with Oil Red O stain on frozen, non-fixed corneal tissue from a falcon.

keratin, and many foreign bodies. This phenomenon is called birefringence.

Other commonly used stains and their use (Fig. 1.12)

- Giemsa or toluidine blue: mast cell granules
- Verhoeff stain: elastic fibers
- von Kossa stain: mineralization
- Prussian blue: hemosiderin or free iron deposition
- Ziehl-Neelsen: acid-fast bacteria
- Tissue Gram's stain: bacteria
- Silver stains for fungi (techniques and names of stains are variable)
- Silver stains for axons (techniques and names of stains are variable)
- Oil Red O for lipid (cannot use paraffin-embedded tissue, alcohol used in fixation and processing removes the lipid).

Immunohistochemical staining techniques

- Detailed consideration of methodology is beyond the scope of this text
- The use of immunohistochemical markers in the diagnosis of specific ocular diseases, including neoplasia, will be highlighted as appropriate throughout the chapters which follow.

Comparative Comments

Immunohistochemical labelling techniques and special stains are in general the same for humans and other animals. The pathologist should be aware of the source of the antibodies in immunohistochemical stains in determining its appropriateness for use in a particular animal.

Chapter 2

Pathologic mechanisms in ocular disease

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OBJECTIVES

- To introduce the terminology and principles used in the morphologic interpretation of general tissue responses to disease
- To present, in a simplified manner, general pathology concepts that need to be considered when interpreting pathological changes in eyes on a routine basis
- To provide an overview of the mechanisms of disease. It is envisaged that the student may return to this chapter when, for example, evaluating a globe with suppurative inflammation, in order to better understand the morphologic features that are used in making that interpretation
- The goal is not to present a detailed discussion of the most basic principles of general pathology, such as cell degeneration or inflammation, which are addressed adequately by other texts.

FUNDAMENTAL CELLULAR AND TISSUE RESPONSES TO INJURY

Pathologic mechanisms in ocular disease are essentially the same for human and veterinary pathology. How they are grouped and taught is largely a matter of style and experience. It can be stated at the outset that the cells comprising the tissue can react to adverse events in several ways, which may be sequential. Depending on the severity and duration of the insult, cell injury may be reversible or irreversible.

The initial response is an attempt at adaptation, with potentially reversible injury, but culminating in cell death if the insult is not remediated.

Even under normal conditions, cells attempt to maintain a steady state, in response to a changing environment; these environmental factors include: changes in workload, levels of hormonal stimulation, and exposure to growth factors and other factors. Comparable adaptive mechanisms also operate in many pathologic conditions, the affected cells becoming altered but remaining viable. These mechanisms include atrophy, hypoplasia and aplasia, hypertrophy and hyperplasia, metaplasia; and dysplasia.

Comparative Comments

The principles discussed in this chapter, regarding cellular degeneration and death, tissue degeneration, inflammation and immunobiology, and abnormalities of cellular or tissue development, are identical in human and veterinary pathology. Similarly, the specific examples of cellular adaptation and reversible and irreversible cell injury in the eyes of humans are extremely similar to those given for other animals' eyes. The causes of injury are multiple, with ischemia and toxicity accounting for most cases in humans.

CELLULAR DEGENERATION AND DEATH

Cellular degeneration

Intracellular edema/hydropic degeneration. Examples include:

- Corneal epithelial cells in corneal edema
- Lens fiber swelling in osmotic cataract
- Toxic change in feline photoreceptors in acute fluoroquinolone toxicity (Fig. 2.1).

Cytoplasmic lipid accumulation/fatty degeneration. Examples include:

- Keratocytes in corneal lipid degeneration (Fig. 2.2)
- Vascular smooth muscle in atherosclerosis.

Hemosiderosis involves accumulation of an intracytoplasmic protein and iron conglomerate that results from the breakdown of hemoglobin. Hemosiderin appears as a brown pigment by microscopy and has a rusty red appearance when seen grossly. Examples include:

- Hemosiderin-laden macrophages, which accumulate within the globe in response to hemorrhage (Fig. 2.3)
- Hemosiderin also accumulates in retinal pigment epithelial cells, ciliary epithelial cells, and in the neurosensory retina following intraocular hemorrhage
- Iron may bind directly to the tissue, especially in the basement membranes of the retinal blood vessels.

Lipofuscinosis involves the intracellular accumulation of a conglomerate containing oxidatively modified lipids. Lipofuscin appears as a light brown granular accumulation in the cytoplasm of affected cells and exhibits autofluorescence. Lipofuscin accumulates as a result of aging or under oxidative stress. Within ocular tissues, lipofuscin is most commonly seen in the retinal pigment epithelium. Examples include:

- Accumulation of lipofuscin in retinal pigment epithelial cells in vitamin E deficiency, or central progressive retinal atrophy/retinal pigment epithelial dystrophy (Fig. 2.4)
- Cytoplasmic swelling in lysosomal storage diseases. There are many hereditary lysosomal storage diseases that affect the eyes of animals. These genetic disorders affect lysosomal enzymatic

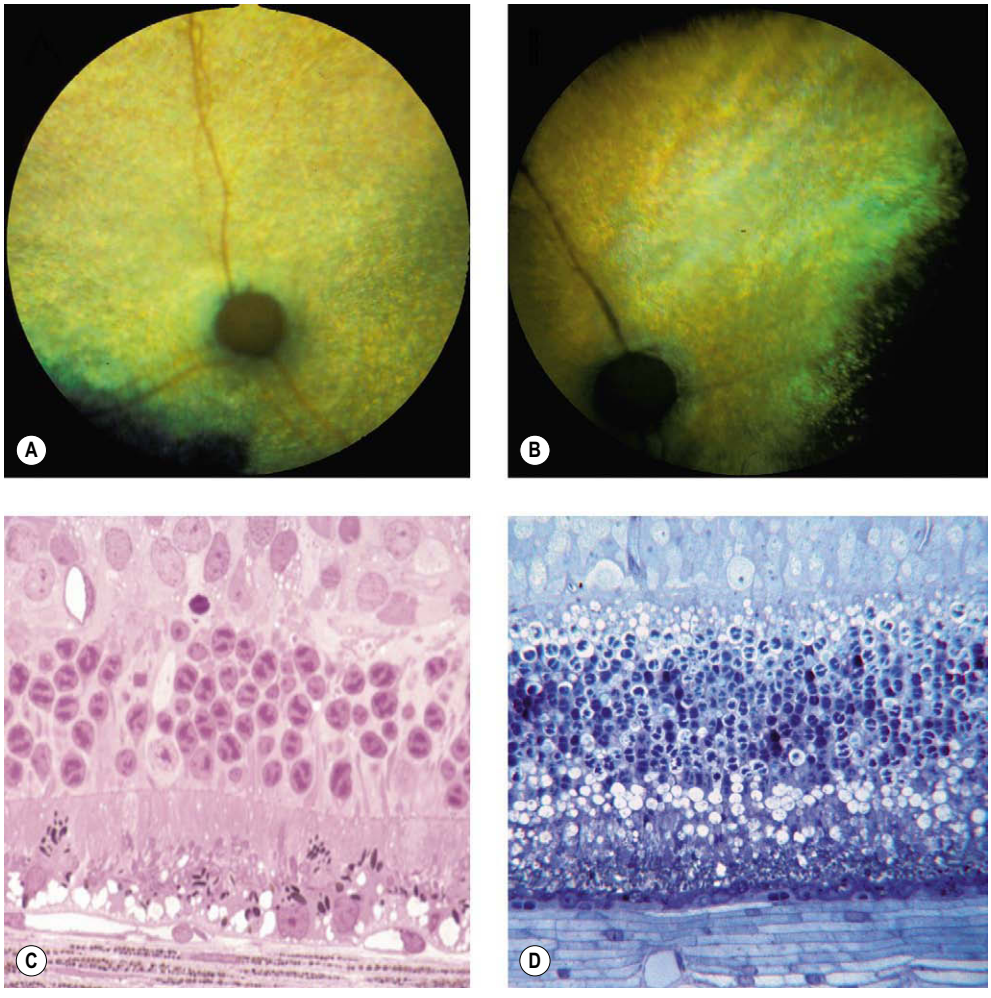


Figure 2.1 Cellular degeneration from fluoroquinolone (enrofloxicin) retinal toxicity in cats. (A,B) Fundus photographs illustrating the clinical appearance of the affected retina. (A) DSH, 14 years old: the temporal hyperreflective tapetum in the left eye is totally void of vessels. (B) DSH, 10.5 years old: blind for 3 months; severe tapetal hyperreflectivity is present. (C) Photomicrograph of the retina showing degeneration of the photoreceptors 90 days after first receiving a toxic dose of fluoroquinolone. (D) Photomicrograph of the retina 3 days after administration of a known toxic dose. There is profound cellular vacuolation of the photoreceptor cells.

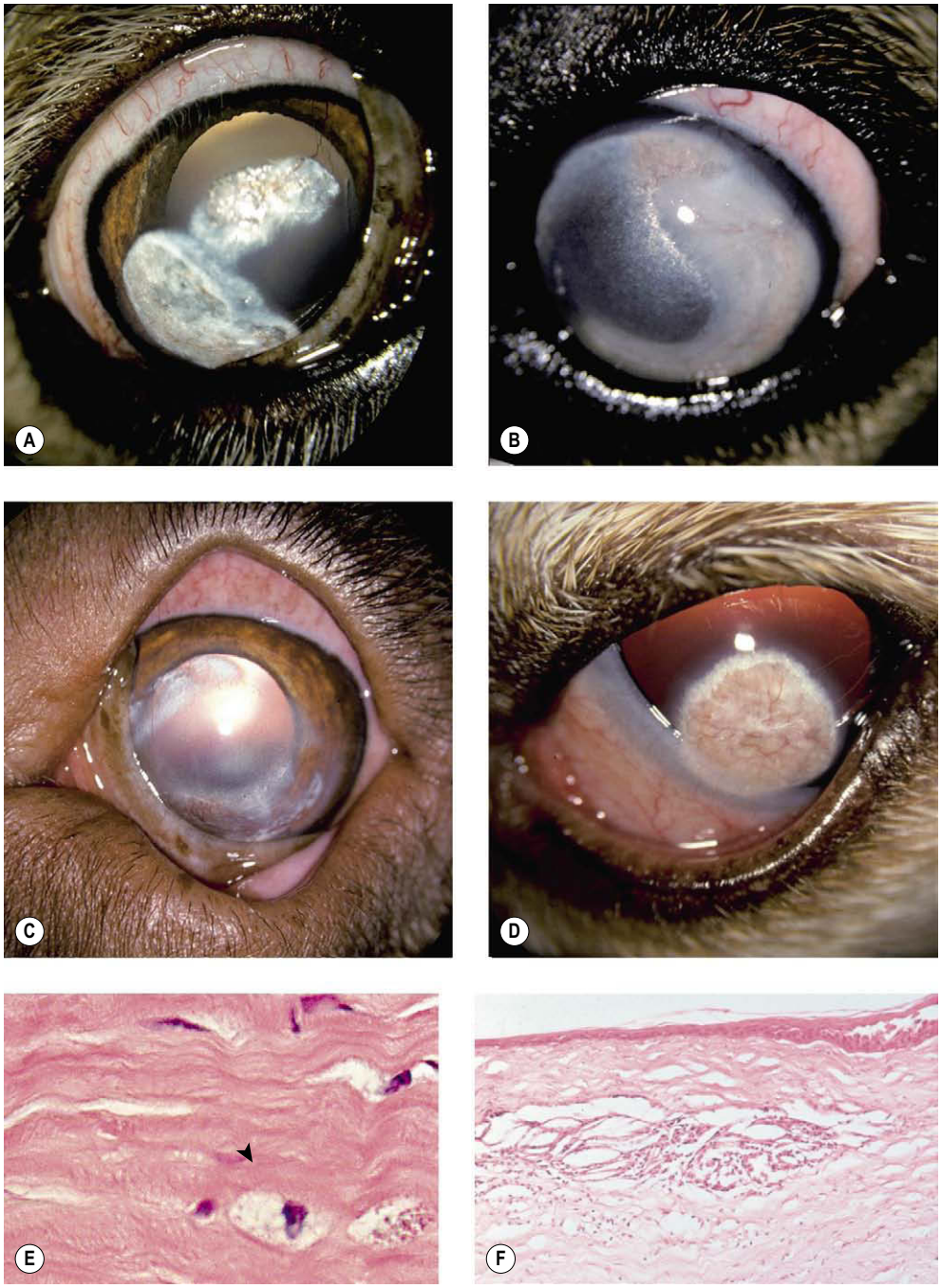


Figure 2.2 Canine corneal lipid degeneration. (A–D) Clinical photographs of canine corneas with lipid deposits. (A) Golden Retriever, 9 years old: white elevated lipid deposits are present bilaterally with fine superficial vessels. (B) Golden Retriever cross, 3.5 years old: lipid deposits can be seen encircling the limbus 360° in this hypothyroid dog. (C) Dogue de Bordeaux, 3 years old: this dog was hypothyroid and has bilateral lipid deposits with superficial corneal vessels. (D) Cockapoo, 5 years old; Axial unilateral lipid deposits with corneal vascularization are present. (E) Photomicrograph showing keratocytes with lipid vacuoles (arrow) in the cytoplasm. (F) Photomicrograph of a superficial stromal cholesterol granuloma.

degradation and, for that reason, lead to the intracellular accumulation of the metabolic by-product that cannot be processed (Fig. 2.5).

Necrobiosis-physiologic cellular degeneration and death of cells

Examples include:

- Lens epithelial cells in the formation of the lens nucleus during normal lens development
- Epithelial keratinization.

Necrosis (oncosis)

The irreversible changes preceding cell death and necrosis are multiple, but certain key elements in all forms of potentially lethal cell injury can be identified: an influx of ionic calcium, a depletion of energy-providing enzyme systems, and an increase in cell membrane permeability.

Such irreversible defects ultimately result in cell death and necrosis through autolysis, as lytic enzymes are released from degenerating lysosomes and as cellular proteins are degraded. Necrosis is characterized by cytoplasmic expansion, followed by disruption of the nucleus, cellular swelling, membrane rupture, loss of organelles, mineraliza-

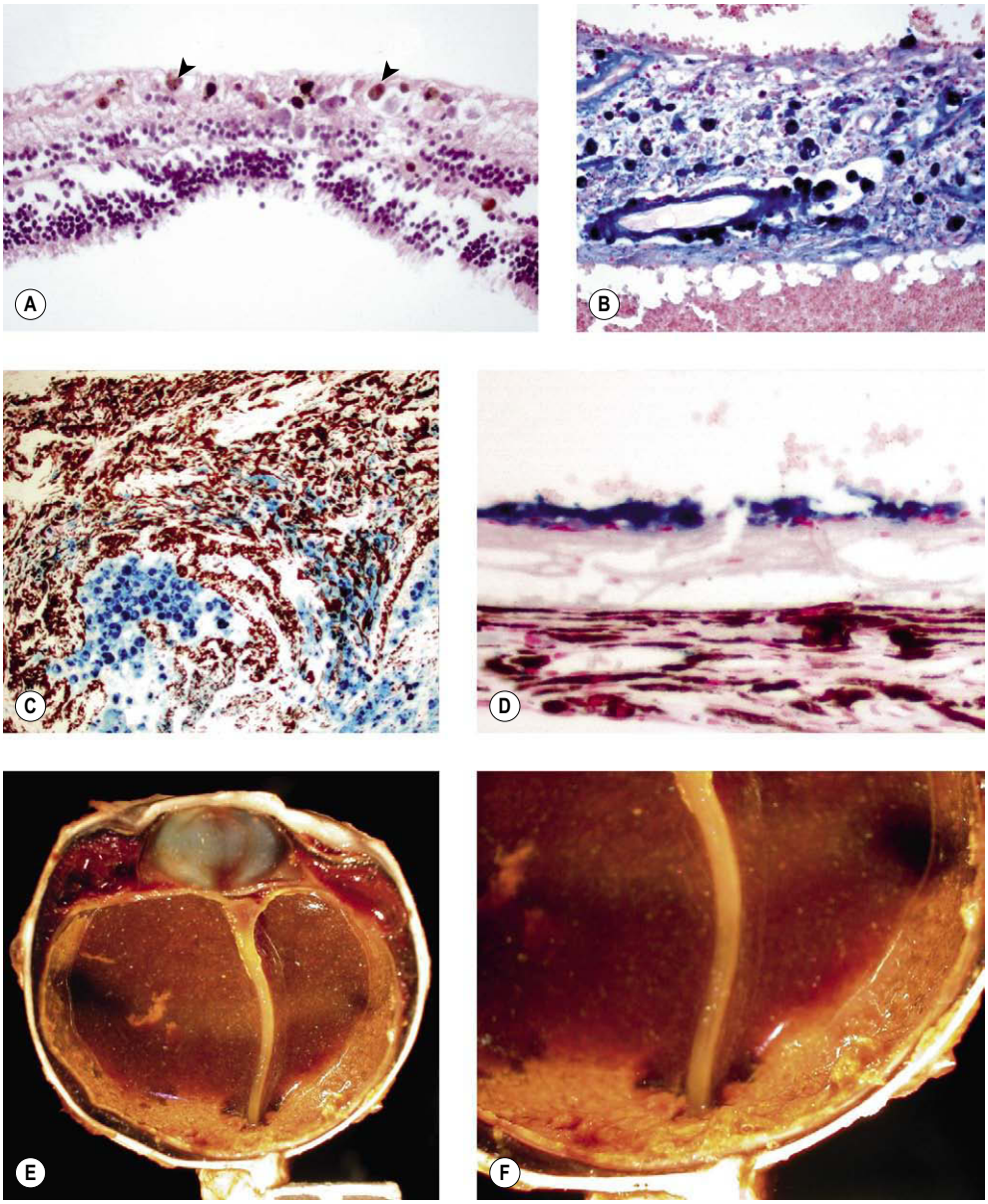


Figure 2.3 Hemosiderosis of ocular tissues. (A) Hemosiderophage cells in the canine retina (arrows). (B) Prussian blue stain of retinal hemochromatosis. (C) Prussian blue stain showing hemosiderophage cells in the iridocorneal angle of a dog. (D) Prussian blue stain showing hemochromatosis of the retinal pigment epithelial cells in a canine eye with longstanding hemorrhage. (E,F) Gross photograph of a canine globe with extensive accumulation of hemosiderin-laden macrophage cells (hemochromatosis), as a result of longstanding hemorrhage into the globe.

tion of the mitochondria, and eosinophilic cytoplasm. Necrosis eventually excites an inflammatory reaction, as the degradative products escape outside the cell. Examples include:

- Necrosis of ganglion cells in the earliest stages of canine glaucoma (Fig. 2.6)
- Necrosis of neoplastic cells deprived of blood supply
- Infarction of retinal tissue after vascular compromise in hypertensive vasculopathy.

Apoptosis (programmed cell death)

In contrast to necrosis, apoptosis is an essentially physiologic means of removing redundant or damaged cells on an individual basis, although it is increasingly being recognized as a feature of a wide variety of pathologic processes. The process of apoptosis is important in the regulation of tissue growth, normal development, and the elimination of damaged and potentially neoplastic cells.

Cells undergoing apoptosis are phagocytosed and removed without exciting a significant leukocytic response. Apoptosis implies the loss of individual cells within viable tissue and is characterized by nuclear pyknosis, autophagocytosis, and rapid digestion of cellular elements by surrounding tissues.

Examples include:

- Rapid retinal degeneration, within days after the first clinically apparent signs of disease, in canine glaucoma (Fig. 2.7)
- Corneal epithelial degeneration in acute bacterial keratitis
- Lymphoma cells in tumors with the 'starry sky' appearance.

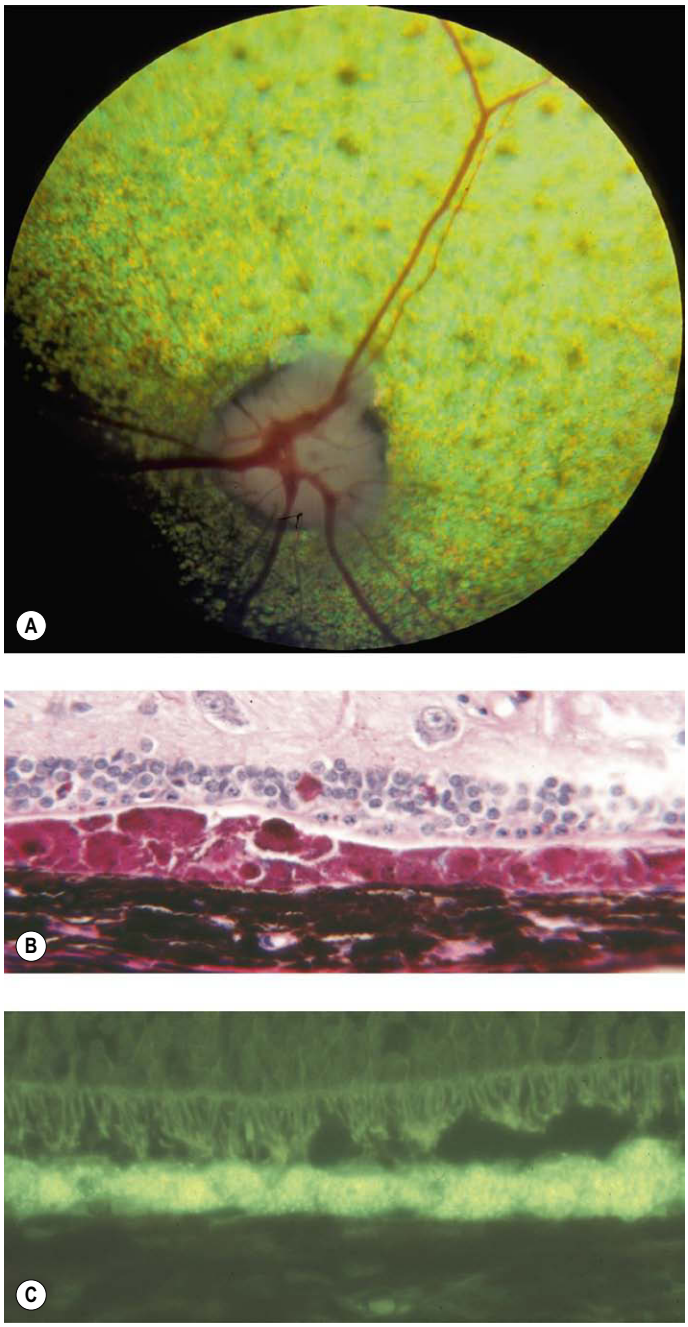


Figure 2.4 Lipofuscinosis. (A) English Cocker Spaniel, 3.5 years old: fundus photograph of a dog with canine lipofuscin retinopathy, characterized by lipofuscin accumulation in the RPE. Subtle tapetal hyperreflectivity with subjective attenuation of vessels is present with multiple focal areas of tapetal pigmentation. (B) PAS stain showing abundant PAS-positive granular lipofuscin in the RPE and loss of photoreceptors. (C) Autofluorescent lipofuscin appears in the RPE when a non-stained section is examined with fluorescent light.

TISSUE DEGENERATION

Edema

Excessive fluid in the extracellular space. Edema may result from vascular leakage in inflammation or vascular disease (Fig. 2.8).

Uveal edema

- The globe has no lymphatic drainage so extracellular fluid in the uvea must be resorbed into blood vessels
- Uveal edema occurs in uveitis.

Corneal edema

The histologic appearance of corneal edema is characterized by:

- A 'washed out' appearance of the corneal lamellae due to stromal edema
- Cytoplasmic swelling (intracellular edema) or expansion of the extracellular space (extracellular edema) within the corneal epithelium.

Corneal edema may result from:

- Vascular leakage or limbal inflammation
- Loss of corneal endothelial cell function
  - The clarity of the normal cornea is related to its relatively dehydrated state that relies on the active pumping of fluid from the stroma into the anterior chamber, by the endothelium, against a pressure gradient
- Relative overload of the endothelial pump
  - At least partly responsible for corneal edema in glaucoma.

Retinal edema

Retinal edema occurs as a result of disruption of the blood retinal barrier.

- The blood retinal barrier is a function of tight junctions in the retinal vascular endothelial cells and tight junctions at the apex of retinal pigment epithelial cells.

Retinal edema results from:

- Hypertensive vasculopathy
- Retinitis, which is often an extension of choroiditis
- Diabetic retinopathy.

Osmotic cataract

Osmotic cataract results when fluid is drawn into the lens by increased osmolarity of the lens fiber cytoplasm due the accumulation of organic molecules such as sorbitol, as seen in diabetic cataract.

Atrophy

Decrease in the volume of a tissue due to decrease in the size and/or the number of the cells that make up the tissue (Fig. 2.9). Characteristics of atrophy:

- Are often associated with a loss of tissue organization
- May be accompanied by fibrosis or gliosis
- May be associated with a change in the nature of the blood supply to the tissue, as in infarction.

Mineral deposition

Mineral deposition may occur in association with tissue degeneration or corneal desiccation. Examples include (Fig. 2.10):

- Chronic cataract
- Band keratopathy – mineralization of the corneal epithelial basement membrane or the adjacent superficial stroma.

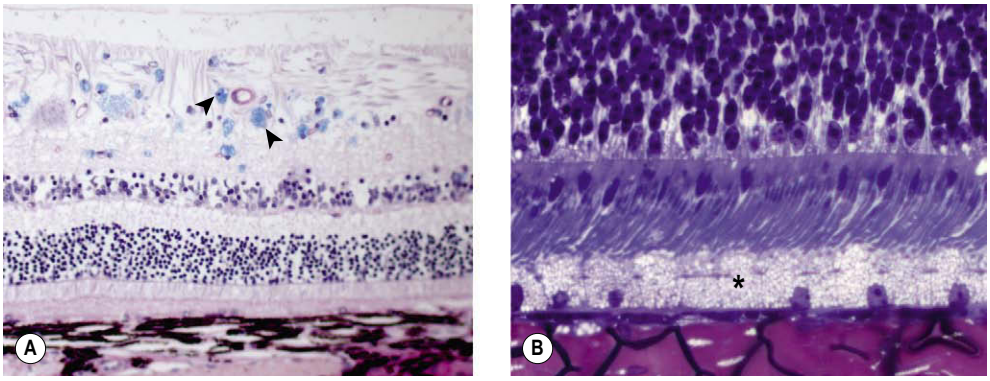


Figure 2.5 Lysosomal storage disease. (A) Photomicrograph of a canine retina stained with Luxol-fast blue showing accumulation of storage product in ganglion cells and glial cells (arrows). (B) Photomicrograph of a bovine retina showing accumulation of storage product in the retinal pigment epithelium (*) in mannosidosis.

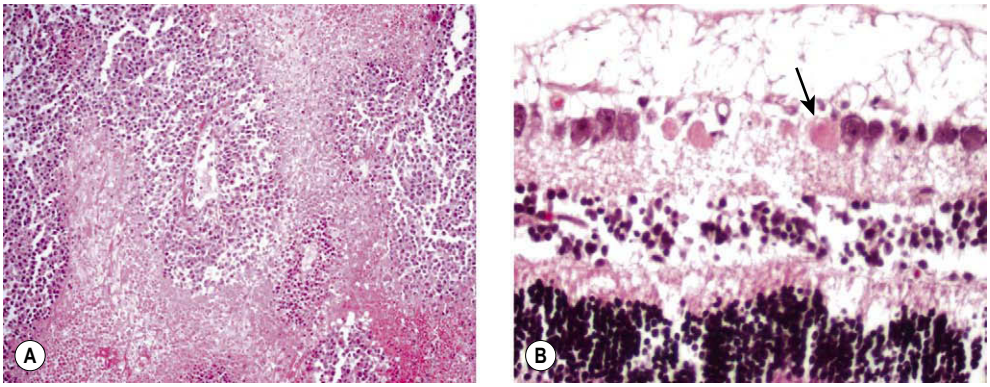


Figure 2.6 Cellular necrosis. (A) Photomicrograph of feline post-traumatic sarcoma, round cell variant. Surviving neoplastic cells are only around blood vessels, and cellular necrosis occurs away from vessels. (B) Necrotic ganglion cell profiles (arrow) in acute canine glaucoma are characterized by excessive eosinophilic staining.

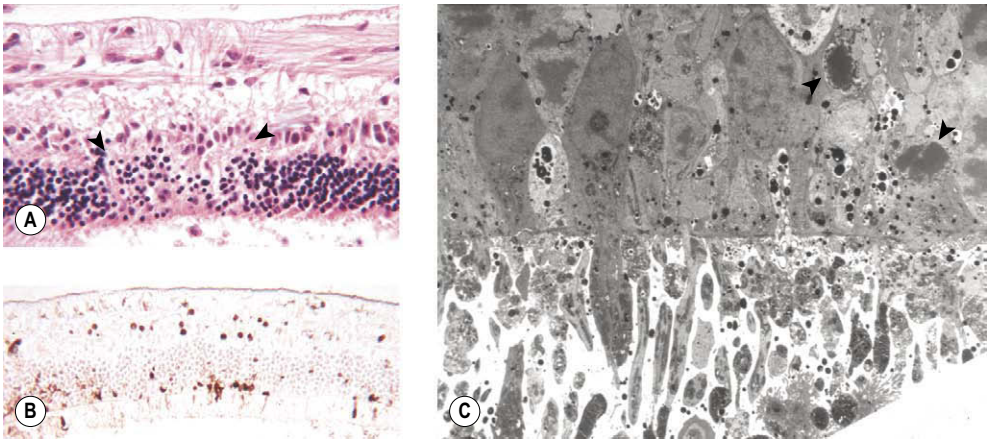


Figure 2.7 Cellular apoptosis. (A) Photomicrograph of the retina from a dog with acute glaucoma showing a regional area of apoptosis of cells in all layers (arrows). (B) TUNEL stain of the retina from a dog with acute glaucoma. The brown marker indicates DNA cleavage in a pattern that is typical of apoptosis. (C) Transmission electron micrograph of a canine retina from a dog with day-4 glaucoma showing apoptotic nuclear profiles (arrows) and extruded nuclear fragments.

INFLAMMATION AND IMMUNOBIOLOGY

Acute inflammation

Morphologic features of acute inflammation (Fig. 2.11) include:

Protein exudation

Leakage of serum protein from blood vessels resulting in:

- Tissue edema
- Proteinaceous exudates within the aqueous, vitreous, or sub-retinal space.

Initiation of the clotting cascade resulting in the formation of fibrinous exudates within the tissues or within the aqueous, vitreous, or sub-retinal space, and recognizable as:

- Deposition of opaque membranous exudates
- Increase in tissue fragility.

Cellular exudation

Suppurative inflammation, with neutrophilic exudate, is a hallmark feature of acute inflammation initiated by bacteria or fungi. Neutrophilic infiltration is often accompanied by macrophage cells that do not form clusters or granulomas (Fig. 2.12). Examples include:

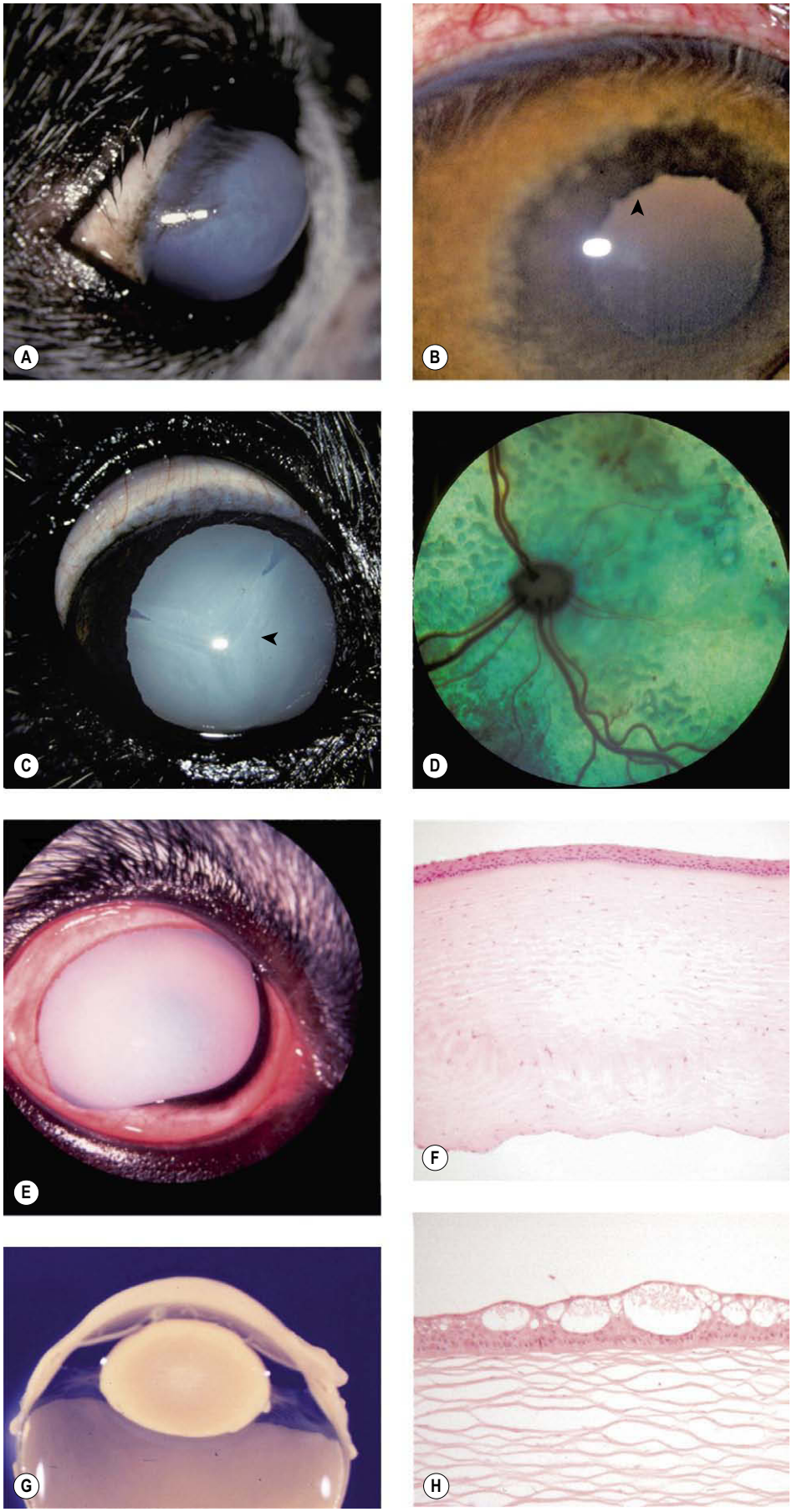


Figure 2.8 Edema of ocular tissues. (A,B) Clinical photographs illustrating corneal edema. (A) Boston Terrier, 7 years old: bilateral endothelial dystrophy led to keratoconus in the right eye. (B) Cocker Spaniel, 5 years old: bilateral idiopathic anterior uveitis resulted in a swollen iris with loss of the normal iris architecture, ectropion uvea (arrow), and mild corneal edema. (C) Miniature Schnauzer, 10 years old: the intumescent cataract in this diabetic produced a wide anterior cortical suture line because of an influx of water (arrow). (D) DSH, 9 years old: fundus photograph showing multiple areas of edema present in the outer retinal layers of this systemic hypertensive cat. (E) Profound corneal opacification in an edematous canine cornea. (F) Photomicrograph showing corneal stromal thickening and the typical 'washed out' appearance of corneal stromal edema. (G) Bouin's-fixed canine globe showing the thickened edematous cornea. (H) Photomicrograph showing bullous change in the corneal epithelium of an affected canine cornea.

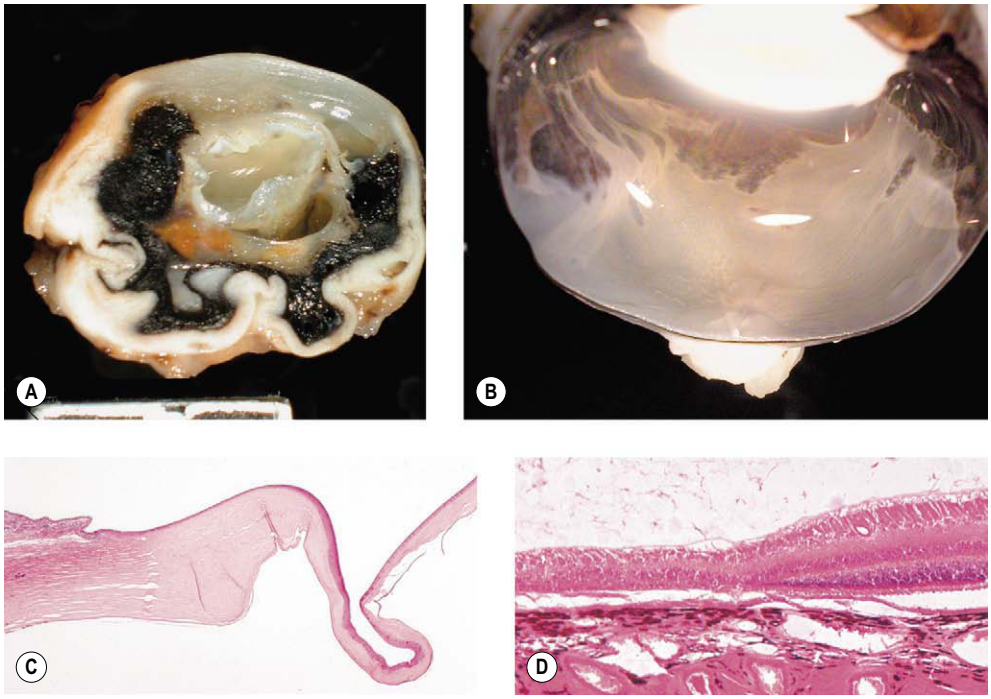


Figure 2.9 Tissue atrophy. (A) Gross image of a canine globe with phthisis bulbi illustrates atrophy and wrinkling of the entire globe. (B) Gross photograph showing segmental peripheral retinal atrophy in a Shih Tzu dog. (C) Photomicrograph of a feline cornea showing atrophy of the axial stroma. (D) Photomicrograph of a cat retina with feline central retinal degeneration showing abrupt segmental photoreceptor atrophy.

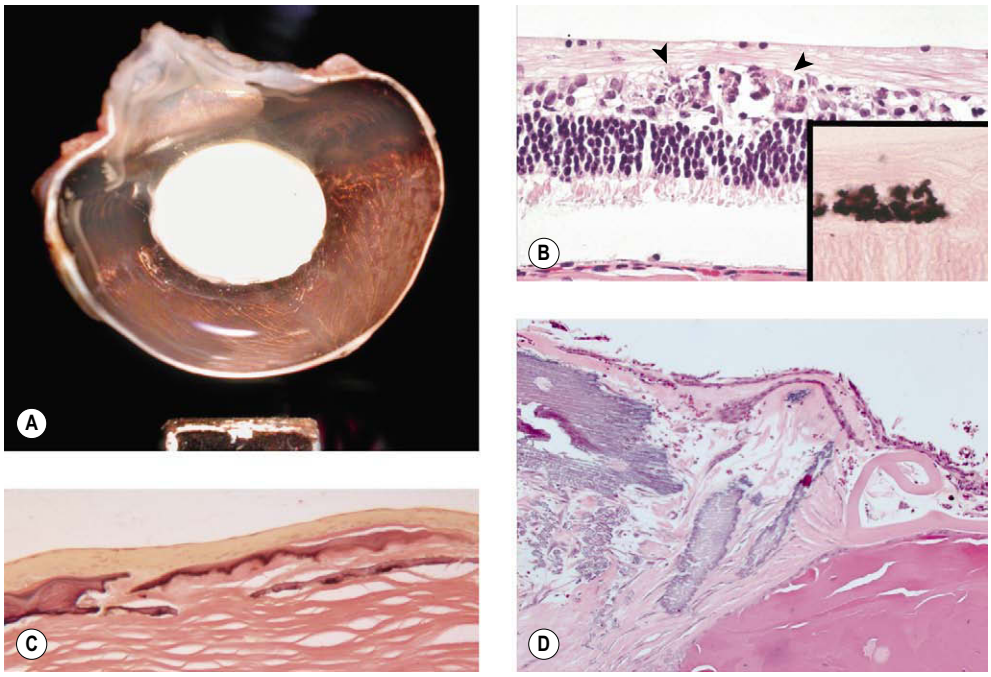


Figure 2.10 Mineralization of ocular tissues. (A) Gross photograph of a canine globe with a mineralized cataractous lens. (B) Photomicrograph of an equine retina with segmental mineralization (arrows) accentuated with the von Kossa stain (inset). (C) Band keratopathy, mineralization of the corneal epithelial basal lamina and superficial stroma (von Kossa stain). (D) Photomicrograph of mineralization in a hypermature cataract in a horse.

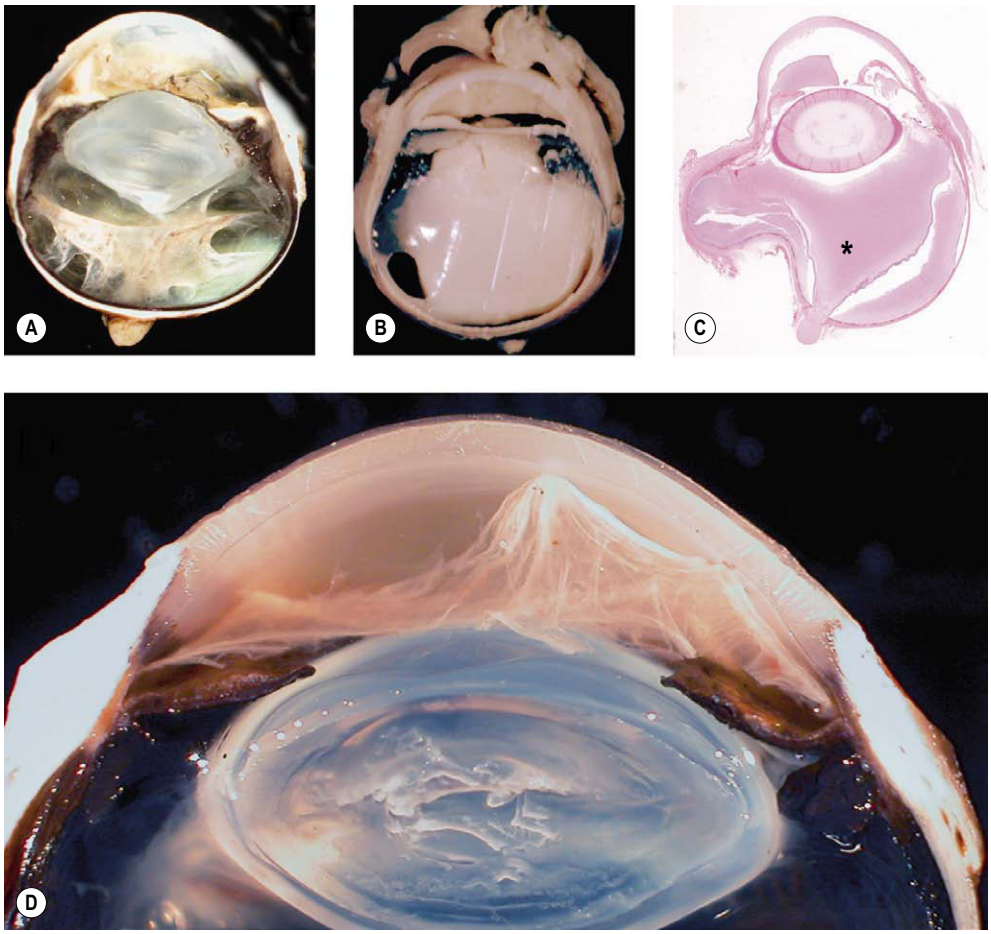


Figure 2.11 Protein exudation in ocular tissues. (A,B) Gross photos of feline eyes affected with feline infectious peritonitis (FIP). The opaque appearance of the vitreous body is due to formalin fixation of the dense protein exudates. (C) Subgross photomicrograph of a feline globe with FIP showing cell poor exudates in the choroid and subretinal space and protein exudates in the vitreous body (*). (D) Gross photograph of a dog eye showing fibrin exudates in the anterior chamber.

- Corneal stromal abscess in mycotic keratitis
- Peri-lenticular exudates in cat scratch injuries, where bacteria are implanted into the lens
- Intraocular exudates from a penetrating injury.

Eosinophilic exudate is a hallmark feature of acute inflammation associated with parasitism or hypersensitivity. Examples include:

- Conjunctivitis or episcleritis due to onchocerciasis
- Eosinophilic conjunctivitis/keratitis in cats.

Macrophage exudation is another feature of acute inflammation, however, macrophages, when present in the form of epithelioid cells are the hallmark of granulomatous inflammation. Examples include (Fig. 2.13):

- Inflammatory cellular response to foreign material
- Inflammatory cellular response to many fungi and some bacteria, such as mycobacteria
- Inflammatory cellular response to exposed lens proteins.

Lymphoplasmacytic, non-suppurative inflammation (Fig. 2.14)

Morphologic features of lymphoplasmacytic inflammation include:

- Perivascular accumulations of lymphocytes and/or plasma cells within intact connective tissues
- Absence of protein exudation or tissue destruction
- Formation of lymphoid follicles within the affected tissues.

Significance of lymphoplasmacytic inflammation

- Indicates chronicity (at least several days)
- Septic disease is not likely to manifest as lymphoplasmacytic inflammation
- Indicative of immune-mediated disease such as:
  - Equine recurrent uveitis
  - Feline lymphoplasmacytic uveitis.

Tissue fibrosis in inflammation

Gross morphologic features of tissue fibrosis include:

- Firmness of affected tissues
- Adhesions within affected tissues
- Loss of color distinctions within affected tissues.

Tissue fibrosis is suggestive of a chronic process (Fig. 2.15).

- When seen in conjunction with acute inflammation, fibrosis defines 'chronic active' inflammation
- The uveal tract resists direct fibrosis; however, the chambers and spaces of the globe (anterior chamber, posterior chamber, and vitreous space) are often affected by fibrosis or fibrovascular proliferation. Examples include: (Fig. 2.16)

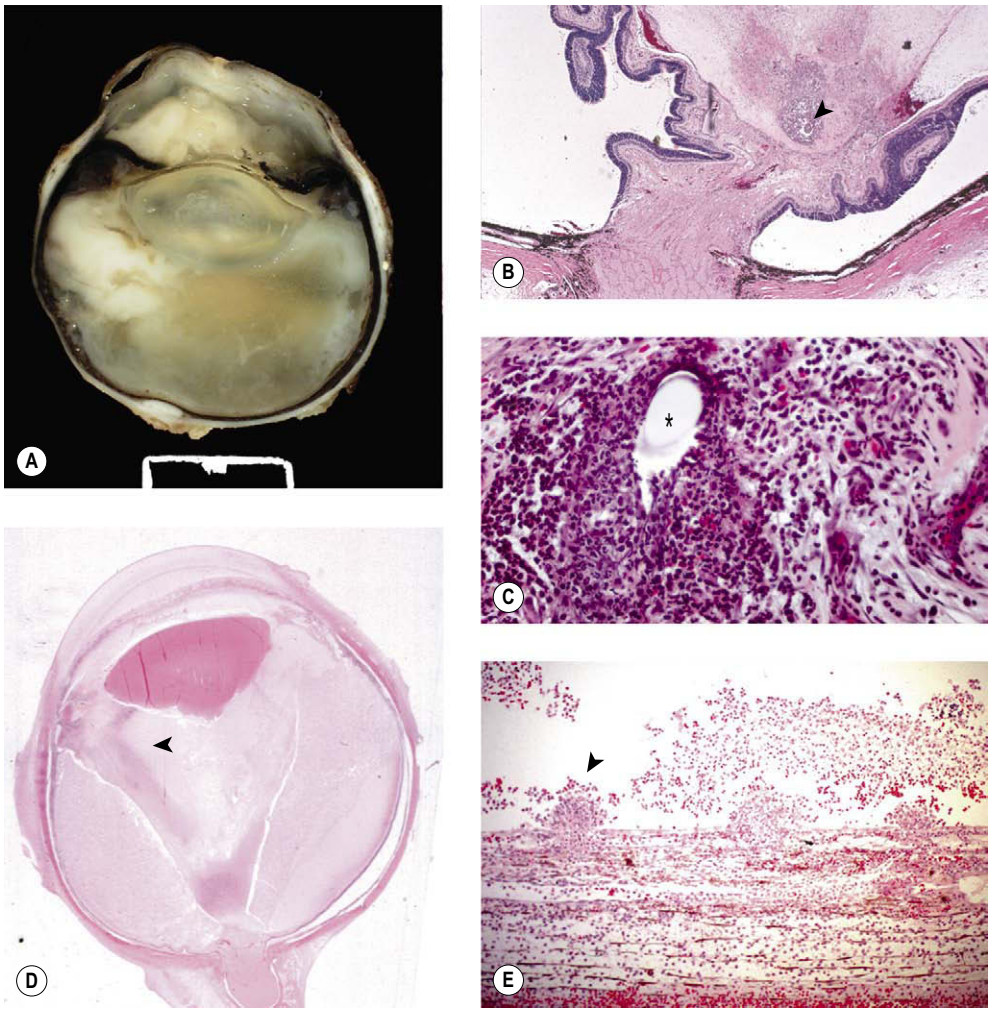


Figure 2.12 Acute suppurative inflammation of ocular tissues. (A) Gross photograph of a canine globe filled with suppurative exudates caused by a penetrating injury. (B) Photomicrograph of a plant foreign body (arrow) embedded in the vitreous body of a dog with suppurative endophthalmitis and retinal detachment. (C) Photomicrograph showing a suppurative infiltrate around a monofilament suture in the peripheral cornea (*). (D) Subgross photomicrograph of a canine globe with suppurative endophthalmitis. The arrow indicates an area of high neutrophilic infiltrate in the vitreous body. (E) Photomicrograph of the choroid in a canine globe with suppurative endophthalmitis secondary to a penetrating injury. There are several neovascular sprouts (arrow) bursting into the subretinal space from the choriocapillaris like 'volcanoes'.

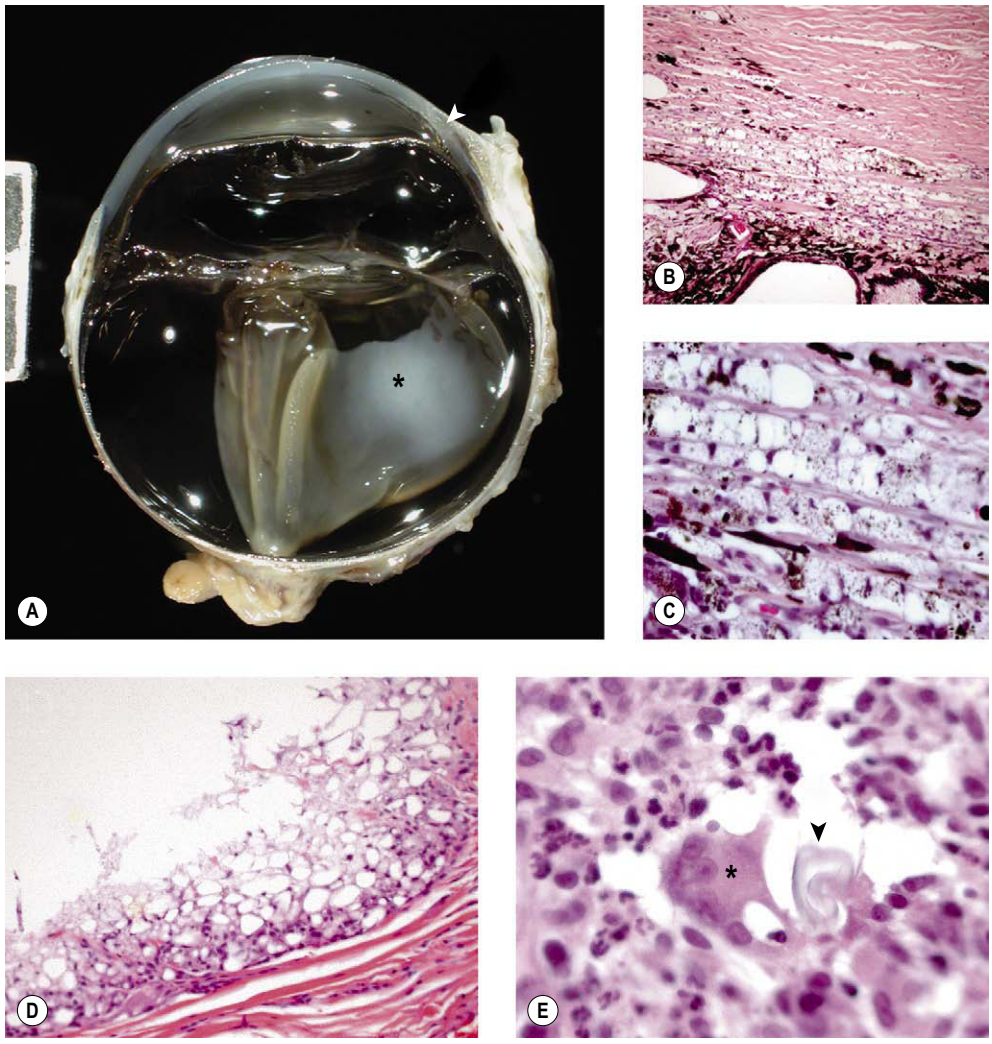


Figure 2.13 Macrophage-rich exudates. (A) Gross photograph of a canine globe with subretinal (*) and anterior chamber exudates rich in macrophage cells. The globe was filled with surgical silicon oil to aid in retinal replacement surgery. (B,C) Photomicrographs from the same dog showing foamy macrophage cells in the iridocorneal angle, where the arrow points in Figure (A). (D) Photomicrograph showing granulomatous inflammation, in the substantia propria of the conjunctiva, which resulted from an injection of methylprednisolone acetate suspension. (E) Pyogranulomatous inflammation centers on foreign material embedded in the conjunctival substantia propria (arrow). A multinucleate giant cell is seen (*).

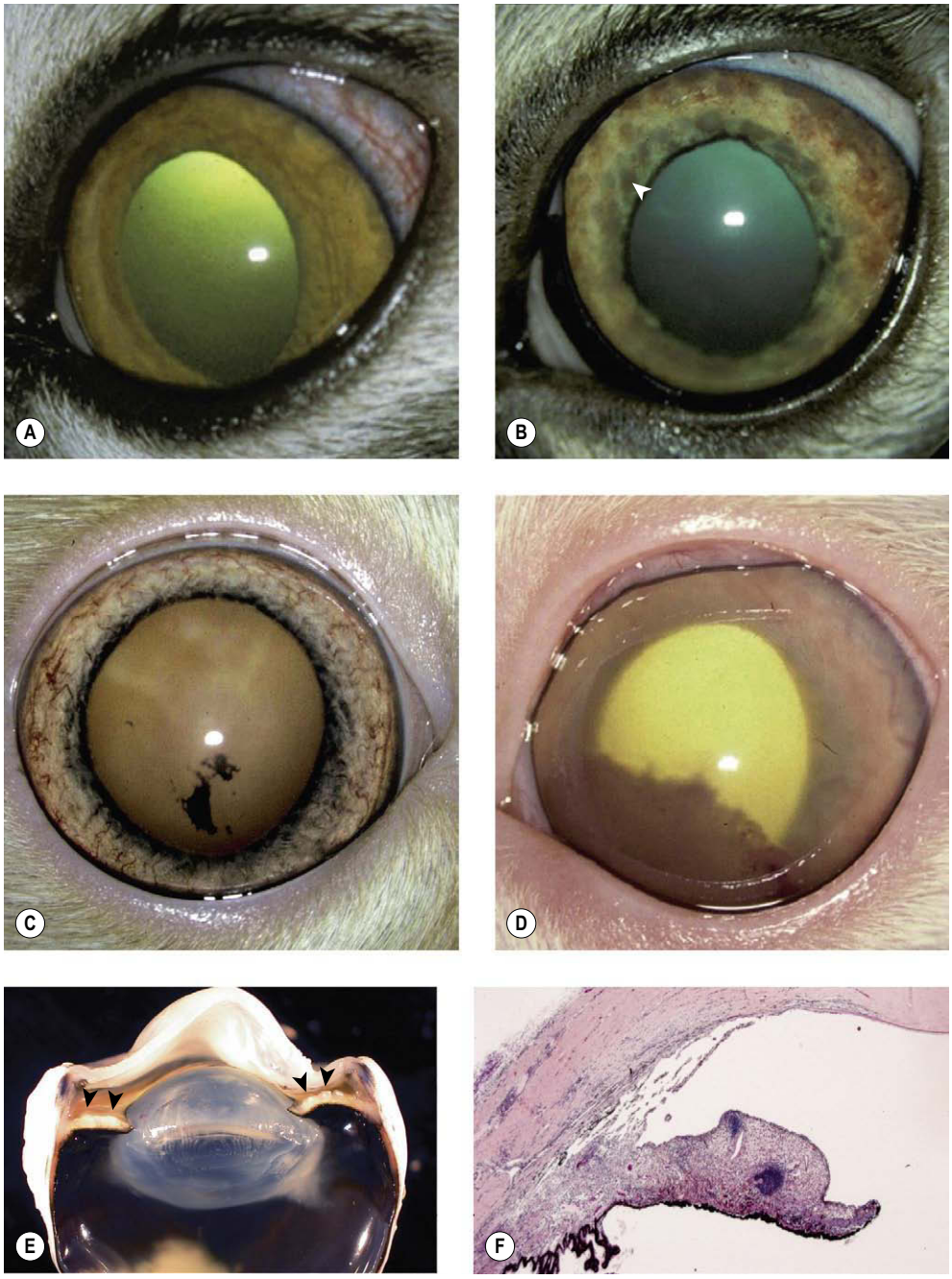


Figure 2.14 Feline lymphoplasmacytic anterior uveitis. (A) DSH, 6 years old: toxoplasmosis was diagnosed, based on serology, as the etiology for the swollen iris and aqueous flare. (B) DSH, 8.5 years old: rubeosis irides and Busacca nodules (arrow) are present. Toxoplasmosis was diagnosed, based on rising serum titers. (C) Persian, 5 years old: rubeosis irides and endothelial pigment are present. The white appearance through the pupil is a total retinal detachment with retinal exudates. Only positive serology was for Bartonella. (D) Ragdoll, 9 months old: severe iritis with aqueous flare and blood-tinged mutton fat precipitates were present in this seropositive Bartonella cat. (E) Gross photograph of an affected cat showing lymphoid follicles in the iris (arrows). (F) Photomicrograph of an affected cat showing a lymphoplasmacytic infiltrate in the iris, including several lymphoid follicles.

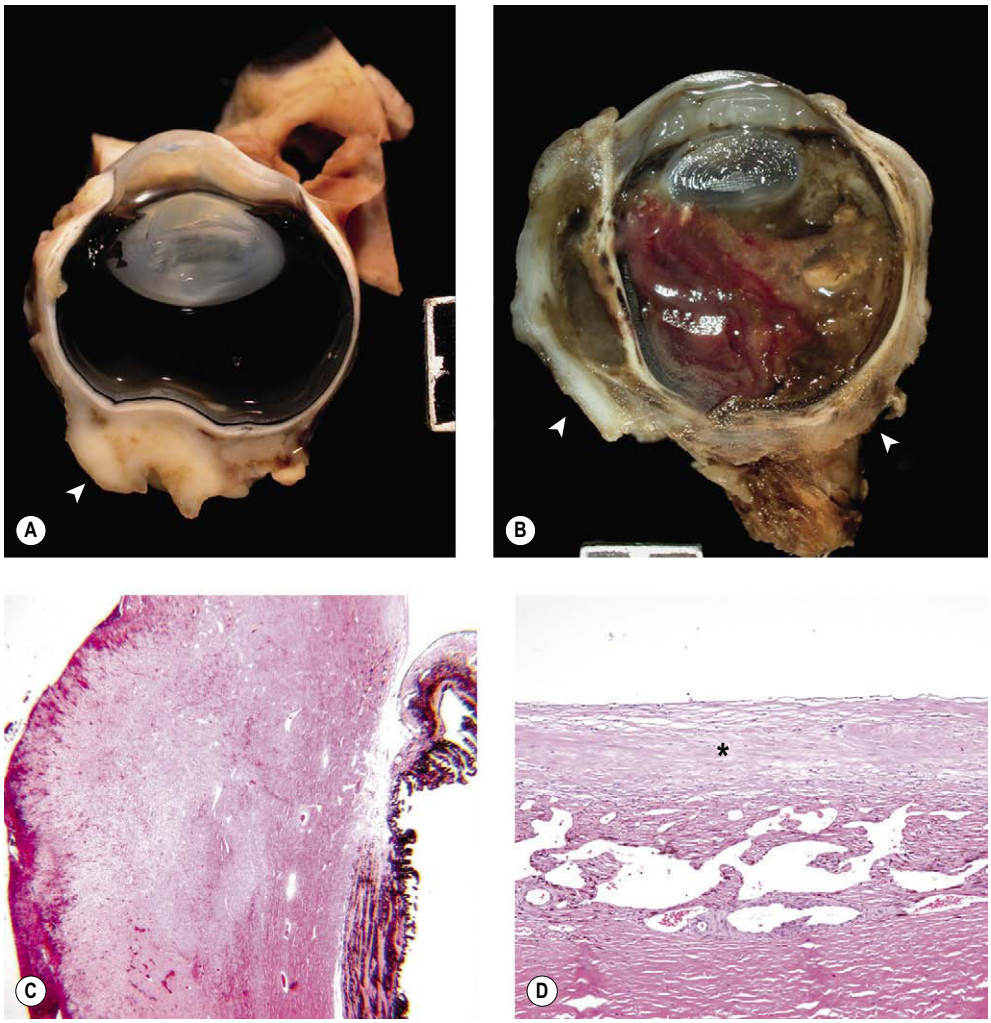


Figure 2.15 Fibrosis of tissues. (A) Gross photograph of the globe from a dog with episcleral fibrosis near the posterior pole (arrow) subsequent to traumatic proptosis. (B) Extensive fibrosis and orbital inflammation (arrows) in a dog with a migrating foreign body. Inflammation extends to the inside of the globe secondary to a penetrating wound (panophthalmitis). (C) Photomicrograph of a dog eye showing fibrosis of the conjunctival substantia propria and limbus following acid burn. (D) Photomicrograph showing idiopathic fibrosis of the inner choroid (*) in a dog.

- Pre-iridal fibrovascular membrane
- Pupillary membrane
- Cyclitic membrane
- Fibrovascular proliferation into the vitreous from the optic nerve head.

Granulomatous inflammation (Fig. 2.17)

Morphologic features of granulomatous inflammation

The diagnostic criteria for granulomatous inflammation are dependent on identifying certain specific features and some pathologists use more restrictive criteria whereas others use more inclusive criteria (Fig. 2.18):

- By the *most restrictive criteria*, granulomatous inflammation is only diagnosed if 'classical' tubercle-like granulomas are seen, such as in tuberculosis
- By *moderately restrictive criteria* (as used in this book), the phagocytic cells should form 'epithelioid' macrophages, forming aggregates with indistinct cell borders in some part of the inflammatory infiltrate
- By the *least restrictive criteria*, granulomatous inflammation is diagnosed any time macrophage cells predominate in the cellular infiltrate, even when the macrophage cells fail to form aggregated clusters of epithelioid cells.

Phagocytic cells identified as epithelioid macrophages may take several different forms (Fig. 2.19):

- Aggregated clusters with features that resemble epithelial cells, hence the name 'epithelioid cell'
- Fusion of phagocytic cells to form multinucleate giant cells which, in turn may be further classified as:
  - Langhans giant cell (peripheral rim of nuclei)
  - Foreign body giant cell (randomly distributed nuclei)
  - Touton giant cell (foamy outer rim of cytoplasm, seen in xanthogranuloma).

Significance of granulomatous inflammation

Suggestive of the persistence of material that is hard to eliminate from the tissues. May be associated with:

- Deep mycoses
- Mycobacteria
- Foreign bodies
- Tissue break-down products
- Idiopathic granulomatous syndromes (commonly encountered in veterinary pathology).

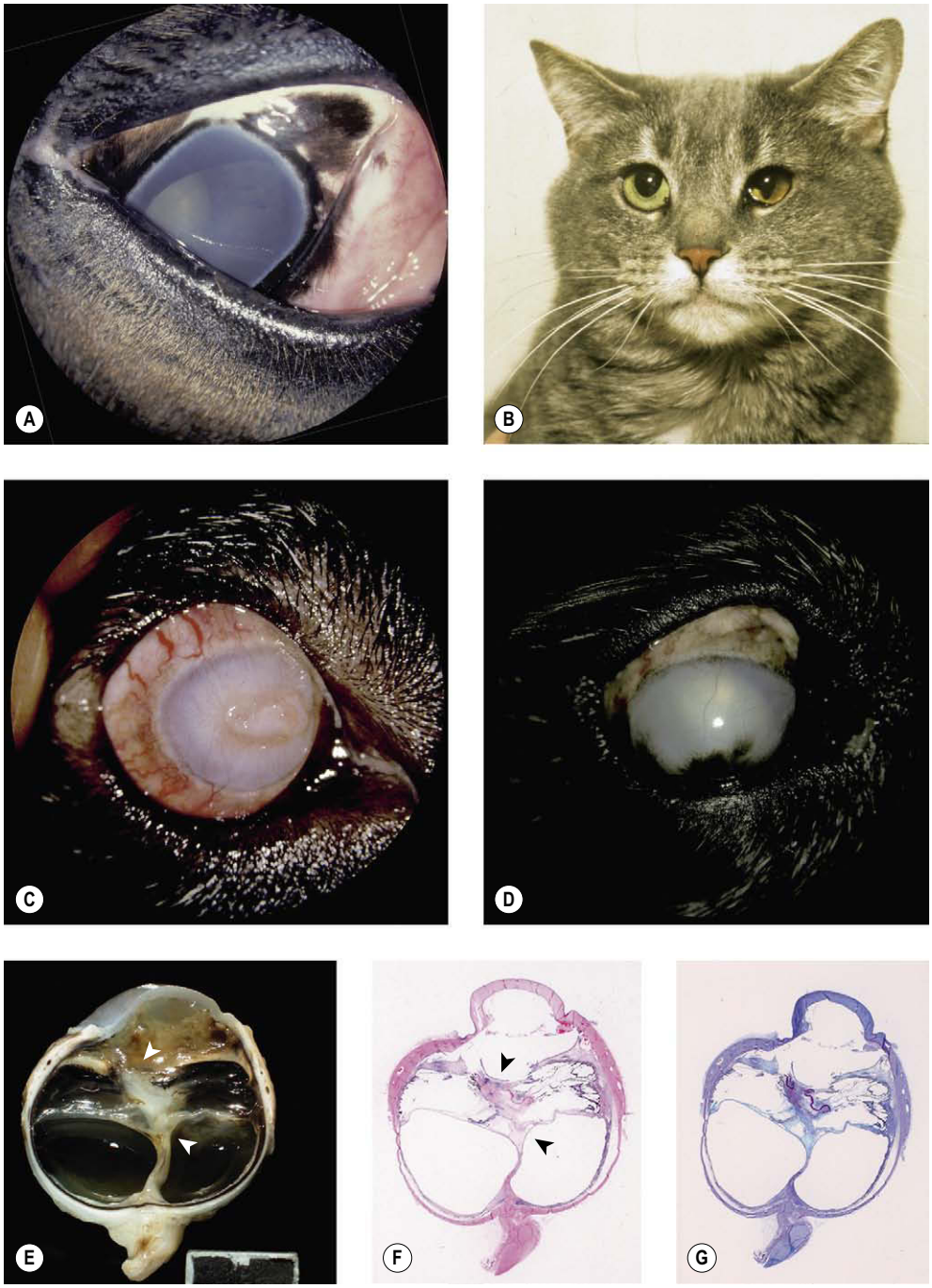


Figure 2.16 Phthisis bulbi, atrophy and wrinkling of the globe. (A) Pony, 1 year old: the right eye was phthisical due to trauma. (B) DSH, 6 years old: the reduced palpebral fissure OS was caused by prior trauma to the globe. (C) Canine Mixed breed, 3 years old: a chronic corneal ulcer and uncontrolled anterior uveitis produced a phthisis bulbi. (D) Cocker Spaniel, 12 years old: a vitreal injection for end-stage glaucoma led to the small hypotensive globe. (E–G) Gross photograph and subgross photomicrographs of a feline globe with phthisis bulbi. The lens capsule is collapsed and fibrosis is pulling the tissues of the globe together (arrows) and towards the center (H&E and trichrome stains).

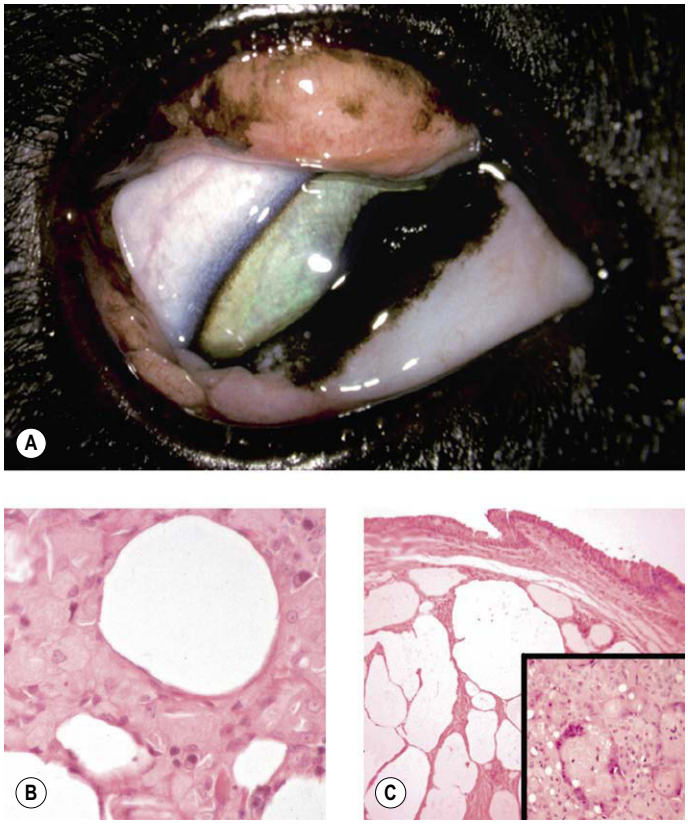


Figure 2.17 Feline lipogranulomatous conjunctivitis. (A) DSH, 2 years old: a firm opaque subconjunctival mass is present in the dorsal and ventral palpebral conjunctiva and visible through the intact conjunctival epithelium. (B) Photomicrograph showing lipid vacuoles and lipophage cells. (C) Photomicrograph showing large 'lipid lakes' and multinucleate giant cells (inset).

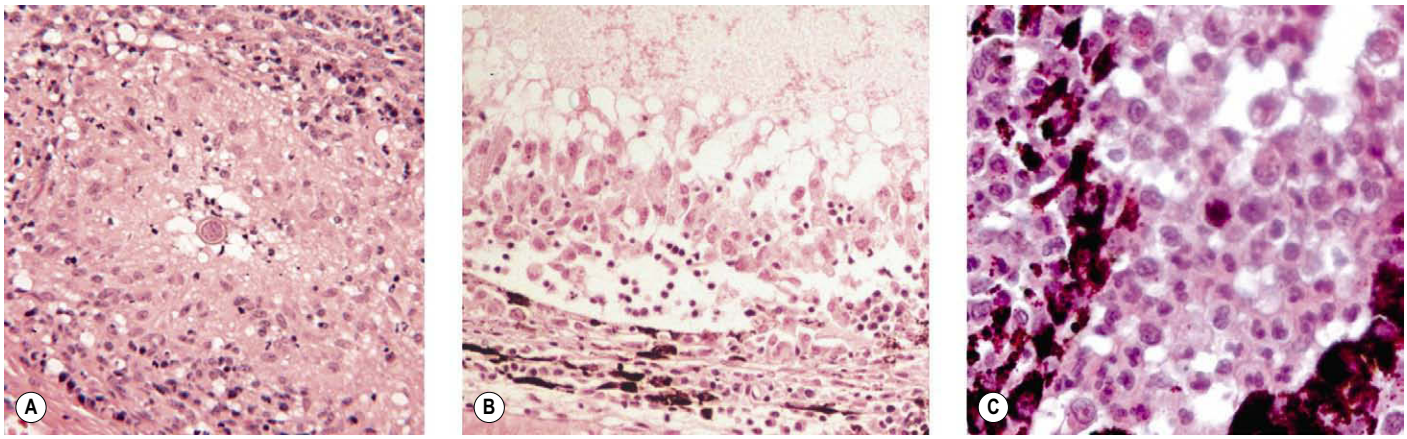


Figure 2.18 Histologic characteristics of granulomatous inflammation. (A) Photomicrograph showing a 'classical' granuloma with a necrotic and suppurative center surrounded first by epithelioid macrophage cells, and then by lymphocytes, plasma cells and fibrosis. This is a dog with chorioretinitis caused by blastomycosis. (B) Photomicrograph showing bands of epithelioid macrophage cells that do not form classical granulomas lining the surface of the pars plana. (C) Loose aggregates of an almost pure macrophage infiltrate in the posterior chamber, but without the characteristics of epithelioid macrophage cells.

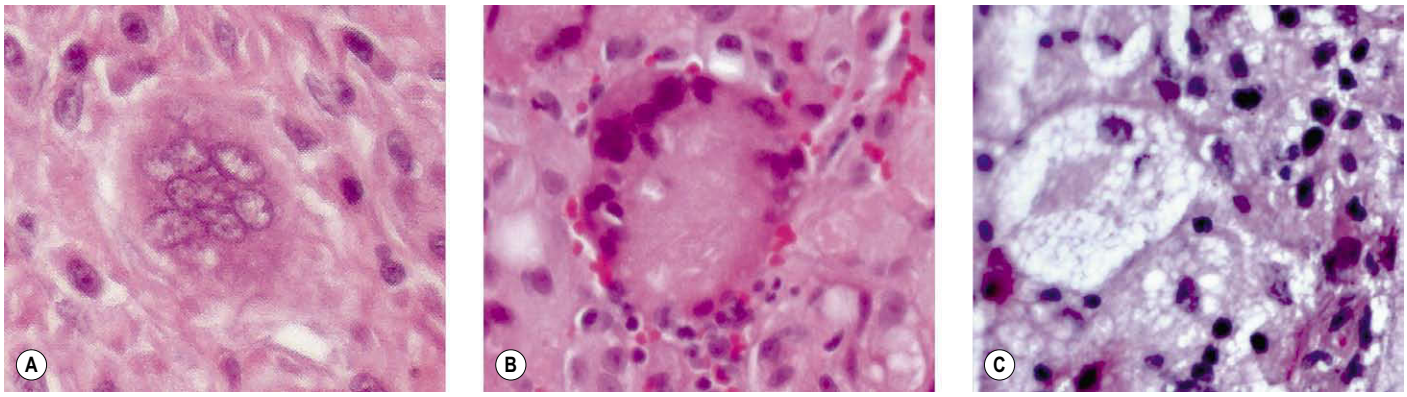


Figure 2.19 Phagocytic multinucleate giant cells. (A) Foreign body giant cell with nuclei pulled to the center of the cytoplasm. (B) Langhans giant cell with nuclei clustered at the cell membrane. (C) Touton giant cell with vacuolated cytoplasm and central nuclei.

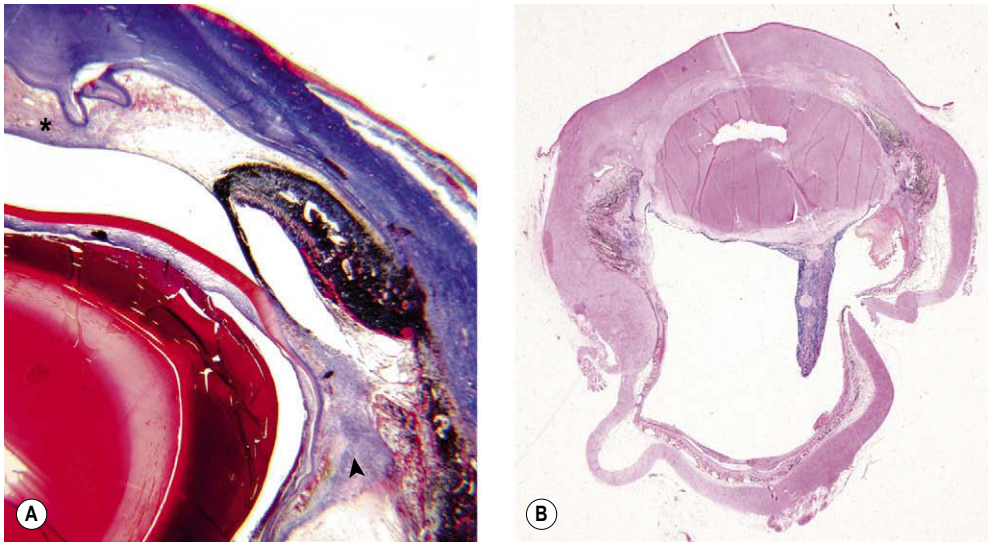


Figure 2.20 Fibrosis in the globe. (A) Low magnification photomicrograph of a canine globe with fibrosis in the anterior chamber (*) and cyclitic membrane (arrow). The uveal tissue is entrapped, but not fibrotic (trichrome stain). (B) Subgross photomicrograph of a canine globe showing extensive fibrosis in the vitreous, anterior chamber and posterior chamber. The entrapped uveal tissue is wrinkled, but not fibrotic.

Immunologic or tissue healing features unique to the eye

- The globe has no lymphatic drainage
- The anterior surface of the eye (i.e. cornea) has no blood supply and is dependant on the physical washing effect of the tear film as well as immunoglobulin and other antimicrobial factors present in tear film
- The tissues of the globe exhibit a deviant immunologic response termed the Anterior Chamber Associated Immune Deviation (ACAID)
  - Soluble antigens injected directly into the anterior chamber impair the ability to develop a delayed-type immune response to that antigen
  - This is associated with a systemic immune deviation, with suppression of the delayed-type hypersensitivity response to the specific antigen, or acquired specific immune tolerance
- Relative resistance of the uveal tract to fibrosis (Fig. 2.20)
  - Fibrosis is often extensive in the anterior or posterior chambers or the vitreous body but not apparent within the uveal tissues directly
  - When fibrosis is seen in the uvea, it is often because there is scleral rupture with fibrosis extending directly from the orbital tissue
- The eyes of neonatal animals subjected to penetrating injury or corneal perforation are remarkably resistant to the development of intraocular inflammation.

ABNORMALITIES OF CELLULAR OR TISSUE DEVELOPMENT OR DIFFERENTIATION

Aplasia and hypoplasia (Fig. 2.21)

Definitions:

- Aplasia: complete failure of a tissue to develop
- Hypoplasia: failure of a tissue to achieve the expected size
- Coloboma: segmental aplasia of one or more of the layers of the globe, leaving a defect. In embryologic terms, typical coloboma occurs when there is a failure of closure of the fetal fissure.

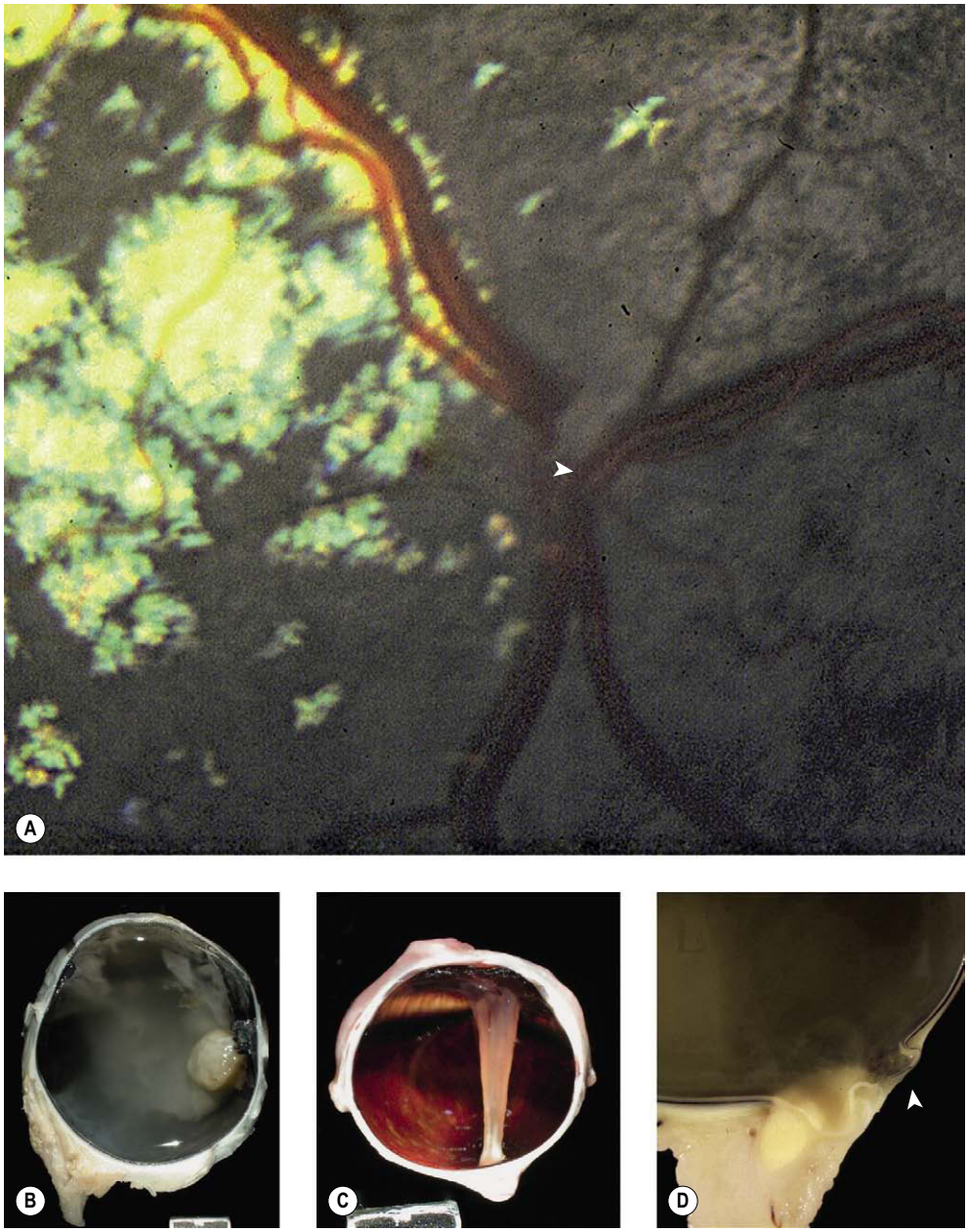


Figure 2.21 Hypoplasia of ocular tissues. (A) Dachshund, 5 months old: fundus photograph of optic nerve hypoplasia. No optic disc can be discerned at the confluence of the major vessels (arrow) in this blind dog. (B,C) Gross photographs of canine globes with hypoplastic lenses (microphakia). (D) Gross photograph of an equine globe illustrates a coloboma (arrow) within and adjacent to the optic nerve head.

Metaplasia

Definition: The abnormal transformation of one differentiated tissue into another. Examples include (Fig. 2.22):

- Osseous metaplasia in chronic trauma
- Squamous metaplasia of the corneal or conjunctival epithelium in response to chronic inflammation.

Dysplasia

Note that the word 'dysplasia' is used in different ways in different circumstances, which may lead to confusion. Two important definitions of dysplasia that are commonly encountered in ocular and general pathology are:

1. Abnormal or disorganized tissue differentiation or development
2. Atypical features of cellular differentiation suggesting neoplasia or a pre-neoplastic state.

Neoplasia

Definition: cellular proliferation with impaired growth regulation leading to distortion or destruction of the normal tissues (Fig. 2.23).

- Benign: a neoplastic lesion that does not carry a risk of metastasis or aggressive infiltration
- Malignant: a neoplastic lesion displaying aggressive local infiltration and causing extensive damage to tissues, disruption of perfusion or distant metastasis.

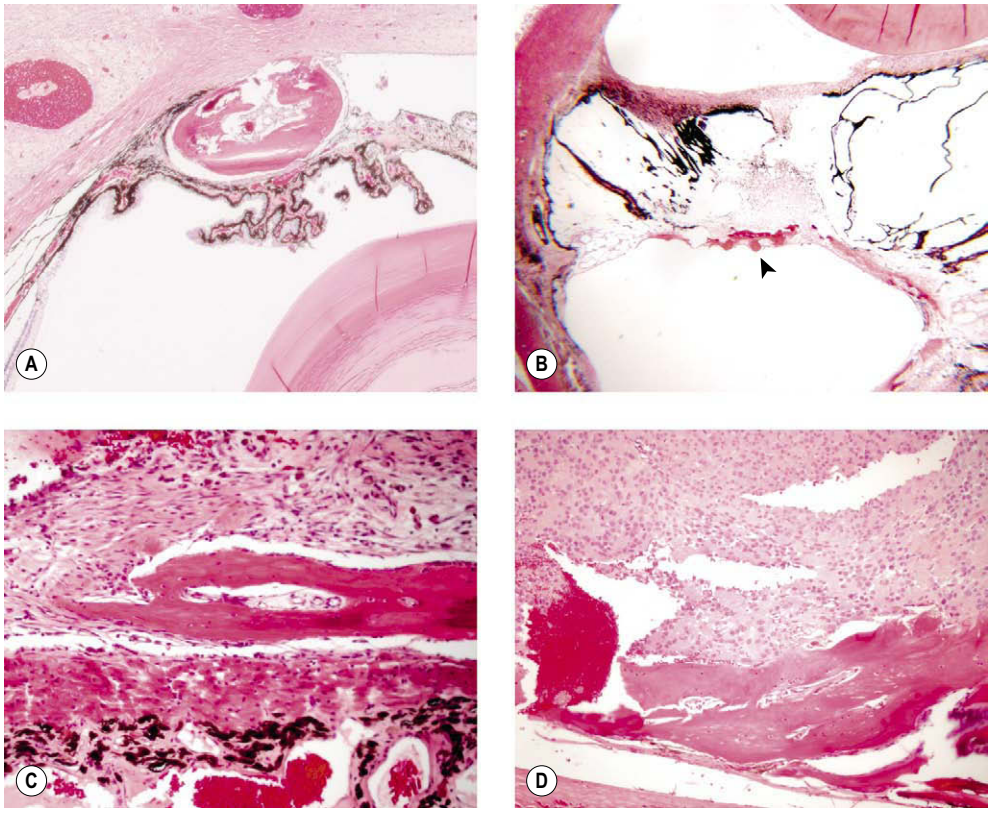


Figure 2.22 Osseous metaplasia in ocular tissues. (A) Photomicrograph of a guinea pig eye showing osseous metaplasia in the ciliary body. (B) Photomicrograph of a feline globe with phthisis bulbi showing osseous metaplasia adjacent to the wrinkled remnants of the lens capsule (arrow). (C,D) Photomicrographs of the choroid from a cat (C) and a dog (D) showing osseous metaplasia adjacent to Bruch's membrane. Both of these animals had long standing ocular disease secondary to trauma.

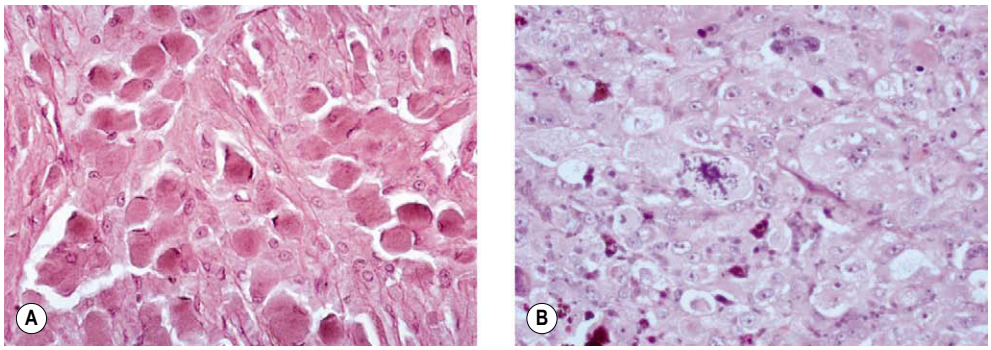


Figure 2.23 Histologic features of benign and malignant neoplasia. (A) Photomicrograph of a bleached section showing a canine benign uveal melanocytoma showing a small, bland, featureless nuclei. (B) Photomicrograph of a malignant uveal melanoma showing features of nuclear and cellular anaplasia and numerous mitotic figures, including bizarre forms.

Aging

Many of the tissues of the eye are at particular risk with respect to the effects of aging because:

- Many ocular tissues are terminally differentiated and have a limited ability to respond to damage.
- By virtue of the function of the eye, ocular tissues are exposed to direct sunlight and, in the case of the retina, focused sunlight
- The outer retina is a highly oxygenated tissue with exposure to oxidative free radicals.

Examples of aging effects on the eye include:

- Progressive thickening of the anterior lens capsule and Descemet's membrane
- Deposition of cell-poor 'glassy' collagenous membrane adjacent to the ciliary epithelium
- Progressive iris atrophy
- Senile cataract
- Cystic degeneration of the neuroepithelia:
  - Typically the peripheral retina in dogs
  - More pronounced in the ciliary body pars plana in cats and horses
- Degenerative changes in Bruch's membrane leading to choroidal neovascularization, an important step in the pathogenesis of age-related macular degeneration in humans.

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Chapter 3

Congenital, developmental, or hereditary abnormalities in animals

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OBJECTIVES

- To illustrate the pathological changes seen in developmental ocular malformations, in a way that is helpful to both the diagnostic pathologist and the clinician who seeks insight into the pathology and pathogenesis of clinically observed lesions
- These cases are infrequently seen in a pathology collection. Of case submissions to the COPLOW collection, 2% are congenital disease or abnormalities of ocular development. Typically, only cases in which the abnormality leads to euthanasia or enucleation are submitted. Examples include:
  - Euthanasia because of other concurrent developmental problems
  - Euthanasia because the affected animal may be considered unsuitable for breeding
  - Euthanasia or enucleation because of disfiguring eye disease
  - Enucleation because of glaucoma
- Almost every species and breed of domestic animal has a list of genetic or presumed inherited diseases which are seen in greater numbers in the specific breeds. However, few of these conditions are regularly sampled for histopathology, and, in general, only those which are represented in the COPLOW collection are presented in this chapter.

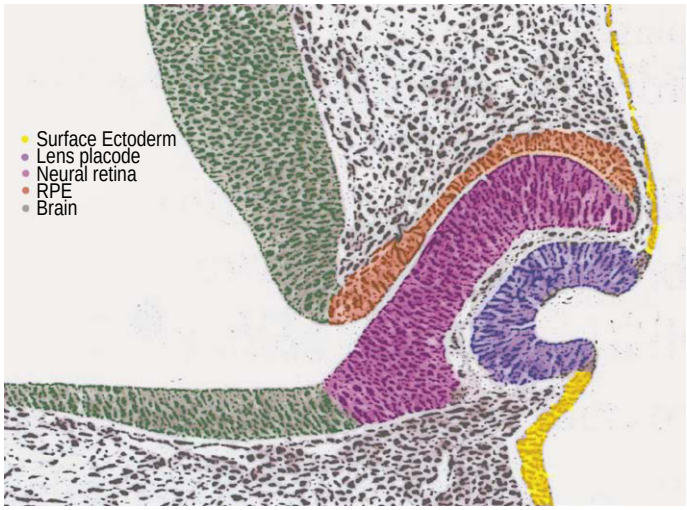


Figure 3.1 Schematic drawing of early embryogenesis of ocular tissues. The lens placode forms and then invaginates in response to the optic vesicle making contact with surface ectoderm. With the subsequent invagination of the optic vesicle to form the double-layered optic cup. (Adapted with permission from Inagaki S, Kotani T 2002 Examination of the rat eye at the early stage of development with osmium tetroxide staining.)

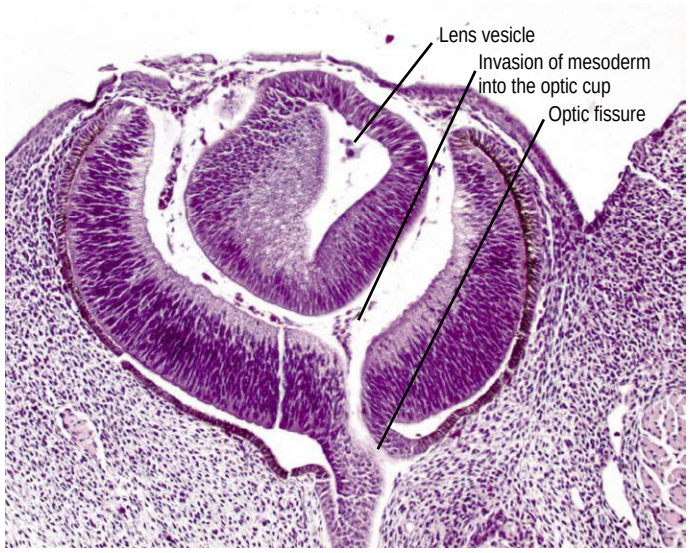


Figure 3.2 Early embryonic eye. Photomicrograph of an embryonic goat eye showing the lens vesicle separated from the surface ectoderm and early stage retinal differentiation. The section passes through the optic fissure, through which mesenchyme enters the developing globe to form the earliest vitreous.

GENERAL PRINCIPLES OF OCULAR EMBRYOLOGY IN RELATION TO SPONTANEOUS DEVELOPMENTAL OCULAR DISEASES (Figs 3.1–3.4)

- The optic vesicle bulges out from the primitive neural tube ectoderm, making contact with the surface ectoderm, thus stimulating the local ectoderm to form the lens placode (Fig. 3.1)
- Lens placode invaginates to form the lens vesicle which separates from the surface ectoderm (Fig. 3.2)
  - Incomplete separation of the lens vesicle leads to developmental abnormalities of the anterior segment, involving the lens, cornea and anterior uvea.
- Invagination of the optic vesicle to form a bi-layered optic cup
  - Failure of normal growth and invagination of the optic vesicle may lead to optic cyst, anophthalmia, microphthalmia, or combined abnormalities of the brain and eye.
- Invasion of vessels and associated mesenchyme into the optic cup to form the primary vitreous and *tunica vasculosa lentis*
  - Failure of the primary vitreous and *tunica vasculosa lentis* to form can lead to microphthalmia
- Sprouting of the neuroepithelium from the anterior margin of the optic cup to form the double-layered ciliary and iridal epithelia (Fig. 3.3)
- Closure of the optic fissure separating the vasculature of the primary vitreous from the mesenchyme outside the optic cup, and establishment of a continuous inner neuroretina and an outer retinal pigment epithelium.
  - Failure of optic fissure closure is one mechanism that can lead to the formation of typical scleral colobomata, usually in the dependant posterior globe

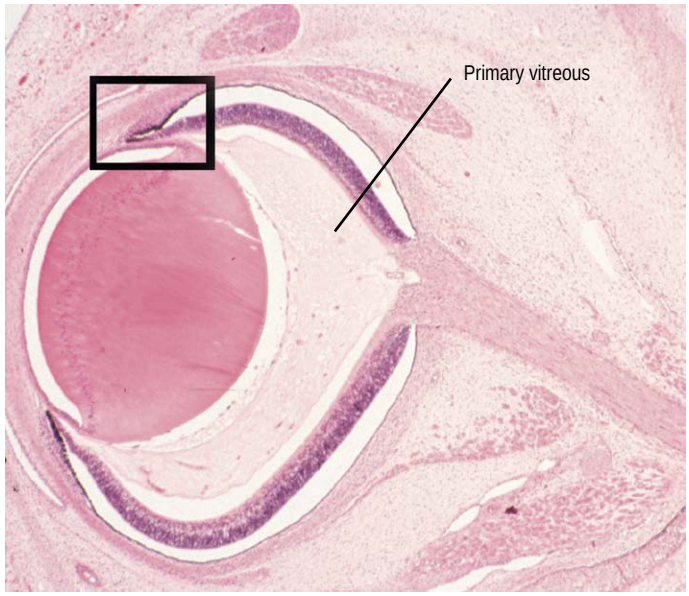


Figure 3.3 Late embryonic eye. Photomicrograph of a bovine embryonic eye showing the primary vitreous, and the forward budding of neural tissue at the margins of the optic cup to initiate development of the ciliary body and iris (box).

  - Colobomatous microphthalmos may result from subsequent failure to establish the intraocular pressure that normally contributes to globe expansion
- Development of a multi-layered neuroretina, extension of retinal ganglion cell axons into the optic nerve, formation of ciliary and iridal epithelia, and the formation of lens fibers and eventually sutures (Fig. 3.4).
  - Failures in the normal development of the retinal and/or uveal neuroepithelia, and lens fibers may be responsible for

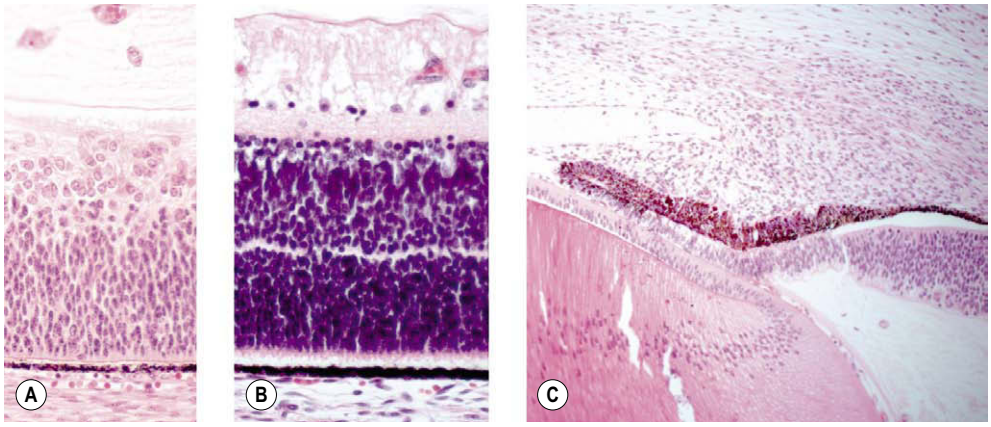


Figure 3.4 Progressive differentiation of the tissues of the optic cup. (A) Photomicrograph of early retinal development before clear differentiation of distinct layers. (B) Photomicrograph showing the development of and separation of the layers of the retina. (C) Photomicrograph showing continued development of the ciliary body and iris by molding and proliferation of mesenchymal tissue.

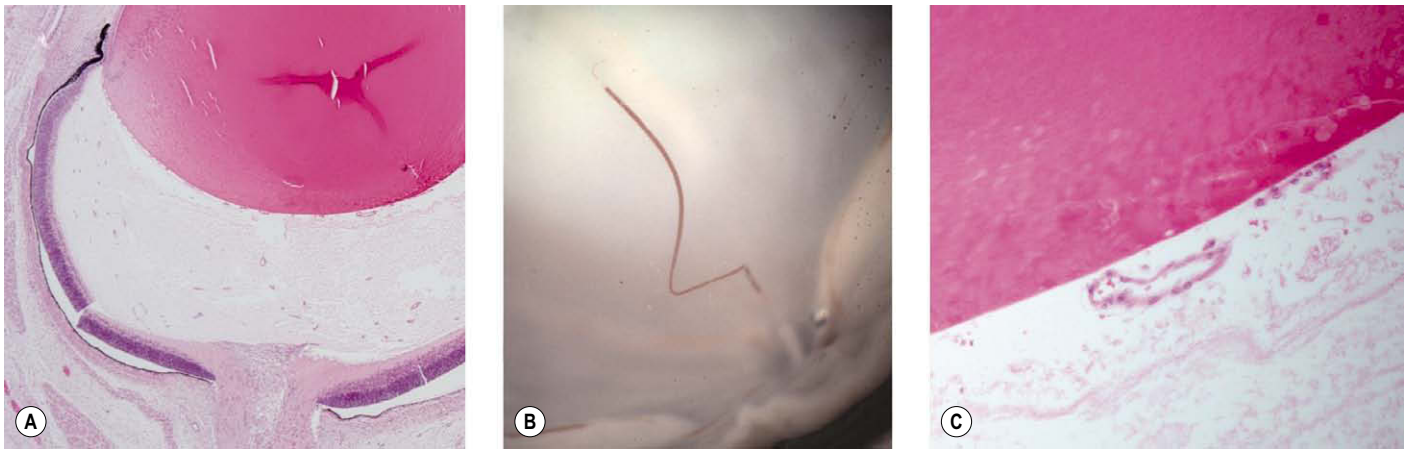


Figure 3.5 Differentiation of the vitreous. Vascular structures in the primary vitreous undergo regression as the primary vitreous is replaced by the avascular secondary vitreous. (A) Subgross photomicrograph showing blood vessels in the primary vitreous. (B) Magnified gross photograph of a neonatal bovine eye showing a vestige of the hyaloid artery. (C) Photomicrograph showing vestiges of the *tunica vascularis lentis*.

retinal dysplasia, optic nerve aplasia/hypoplasia, uveal colobomas and congenital cataract, respectively.

- Establishment and remodeling of the stromal layers of the eye including the uveal, scleral, and corneal stroma
  - Failure of this normal mesenchymal development may be responsible for goniodysgenesis, choroidal hypoplasia, persistent pupillary membrane, Peter's anomaly, variations in uveal pigmentation, and some colobomatous lesions
- Regression of the hyaloid vasculature of the primary vitreous and *tunica vasculosa lentis* and formation of the secondary vitreous (Fig. 3.5)
  - Abnormalities in this process are associated with persistent hyperplastic primary vitreous, persistent hyperplastic *tunica vasculosa lentis*, and persistent hyaloid artery, as well as vitreoretinopathies such as vitreoretinal dysplasia.
- Vascularization of the retina, and the continued development of retinal ganglion cells and their axons, which enter the optic nerve (Fig. 3.6)
  - Failure of these processes leads to neovascular sprouting into the vitreous and optic nerve hypoplasia, respectively.
- The full development of a multi-layered retina with functional and differentiated photoreceptors (this process continues after birth) (Fig. 3.7)
  - Failure results in retinal dysplasia or photoreceptor dystrophies.

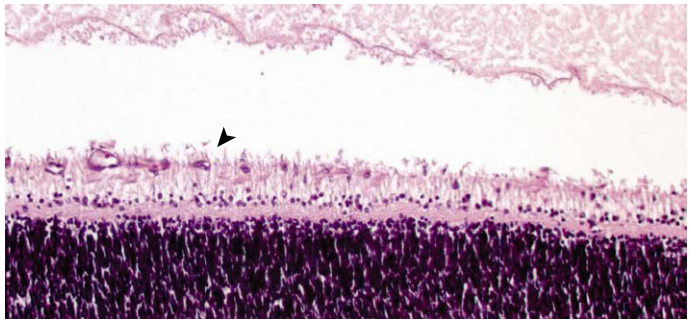


Figure 3.6 Retinal blood vessel growth. Photomicrograph of a neonatal canine retina showing retinal blood vessel proliferation and differentiation. The arrow points to a newly formed vessel in the developing nerve fiber layer.

- Many of the ocular tissues continue to develop throughout the early post-natal period, or, as in the case of the lens, throughout life. Abnormalities of these processes can lead to diseases that are not manifest in young animals, e.g. many forms of inherited cataract, hence they will not be covered in this chapter.

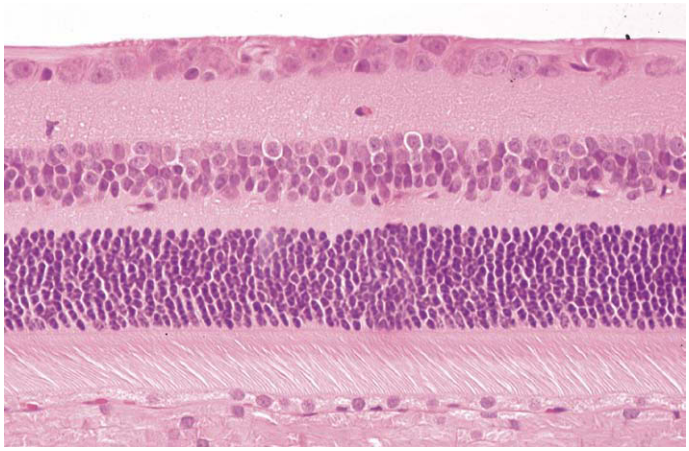


Figure 3.7 The fully-differentiated feline retina in the area centralis. Photomicrograph of the normal, fully-differentiated feline retina sampled in the area centralis, the region with the highest density ganglion cells.

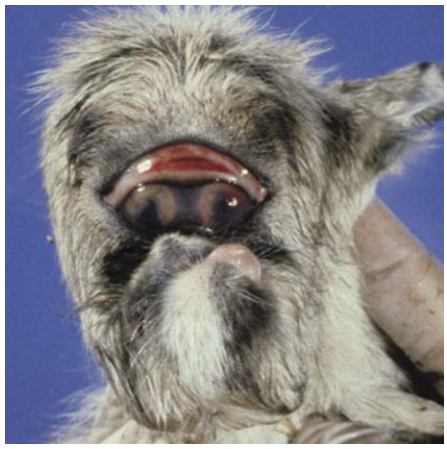


Figure 3.8 *Veratrum californicum* induced teratogenesis. A neonatal lamb has toxic synophthalmos, caused by maternal ingestion of *Veratrum californicum* on day 14 of gestation. (Courtesy of Ron Riis, Diplomate – American College of Veterinary Ophthalmology).

Comparative Comments

These general principles of ocular embryology apply to humans as well as other vertebrates. Specific congenital abnormalities in the human eye will be considered in the chapters which follow, discussing specific tissues within the eye and in the orbit and adnexa.

The various congenital anomalies arise because of variation in size, location, organization, or amount of tissue that represents a departure from normal.

A number of congenital abnormalities in humans fall under the classification of hamartomas or choristomas.

- A hamartoma is an excessive amount of mature tissue (hypertrophy and/or hyperplasia) occurring in a location in which that tissue is usually found. An example of a hamartoma would be any of the hereditary phakomatoses such as neurofibroma (a mass of mature neural tissue and fibroblasts) occurring in the orbit. No such collection of congenital disorders is described in animals
- A choristoma, in contrast, consists of normal, mature tissue in an abnormal location. Embryologically, this is a result of one or two germ layers forming mature tissue that is not normally found in that topographic location. An example of a choristoma is lens occurring in the lid (a phakomatous choristoma).

ABNORMALITIES ASSOCIATED WITH INFECTIOUS DISEASES OR MATERNAL INTOXICATION

Cyclopia or, more correctly, synophthalmos, in lambs, *Veratrum californicum* toxicity (Fig. 3.8)

- This is caused by consumption of alkaloids from the weed *Veratrum californicum* (Western False Hellebore) by the pregnant ewe on day 14 of gestation
- The 14 day embryo is undergoing gastrulation to form a neural tube with lateral symmetry
- Affected lambs have numerous developmental anomalies of the face, including arhinencephaly characterized by a proboscis-like nose developed above the fused globes
- Arhinencephaly with synophthalmos in humans is associated with very similar facial and ocular anomalies but no single teratogenic association has been made.

Abnormal ocular development in cattle associated with maternal infection with bovine viral diarrhea – mucosal disease (BVD-MD) virus (Figs 3.9 & 3.10)

- Caused by a pestivirus
- In post-natal infection, the virus causes a necrotizing epitheliotropic disease characterized by diarrhea
- Infection of the fetus is associated with several syndromes
  - Early maternal infections (before 40 days' gestation) results in infertility, or fetal death and resorption
  - Infections later may be associated with abortion
  - Infection after 40 days gestation can result in normal, immune-deficient, or stunted calves that are immune-tolerant of the virus and remain persistent carriers of the virus. These calves are of great importance in the spread and control of the disease
  - Some calves infected after 40 days' gestation develop congenital abnormalities (Fig. 3.9)
    - Cerebellar hypoplasia 'dummy calf'
    - Brachygnathia
    - Ocular abnormalities, typically seen in calves infected later than 76 days but before 150 days gestation, include:
      - Microphthalmos
      - Microphakia/cataract
      - Retinal detachment
      - Retinal atrophy/dysplasia
      - Spindle cell metaplasia of the retinal pigment epithelium
      - Immunohistochemistry for BVD-MD virus antigen shows staining in blood vessels and punctate staining in the outer plexiform layer (Fig. 3.10).

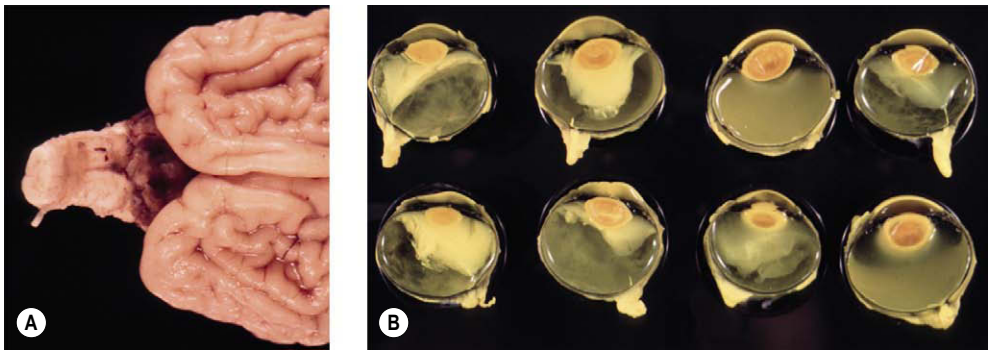


Figure 3.9 Teratogenic effects of maternal infection with bovine virus diarrhea (BVD). (A) A neonatal calf brain showing profound hypoplasia or atrophy of the cerebellum. (B) Gross photograph showing both eyes from four affected calves with microphthalmos, protein exudation and lens displacement.

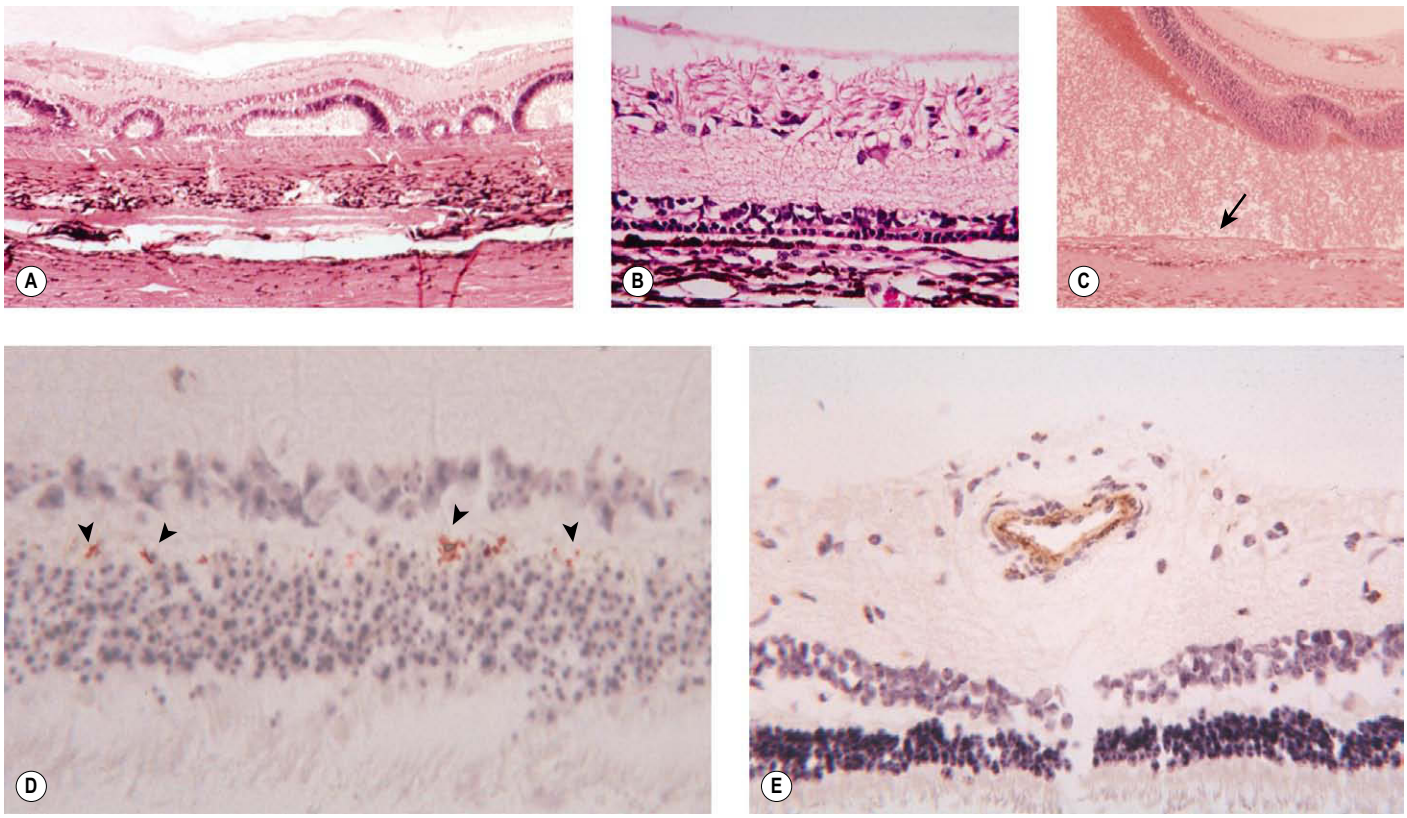


Figure 3.10 Retinal changes seen in congenital BVD infection. (A) Dysplastic retinal development. (B) Outer retinal (photoreceptor) hypoplasia. (C) Redundant spindle cell tissue proliferates from the metaplastic retinal pigment epithelium (RPE) (arrow). (D) BVD immunohistochemistry labels foci in the inner plexiform layer (arrowheads). (E) BVD immunohistochemistry labels blood vessels.

Retinal dysplasia associated with perinatal infections in dogs and cats

- In cats infected *in utero* with feline panleukopenia virus retinal dysplasia is frequently associated with cerebellar hypoplasia
- Retinal necrosis and dysplasia have been reported following experimental infection with feline leukemia virus
- Dogs surviving neonatal canine herpesvirus infection demonstrate retinal dysplasia, necrosis and degeneration, often associated with other ocular abnormalities related to panuveitis.

Comparative Comments

The principle infectious embryopathies in humans are congenital rubella syndrome (Gregg's syndrome) consisting of cataracts, cardiovascular defects, mental retardation, and deafness; cytomegalic inclusion disease; congenital syphilis; and toxoplasmosis.

The major drug embryopathies associated with a variety of eye changes in humans are: fetal alcohol syndrome, maternal thalidomide ingestion during the first trimester of pregnancy, and lysergic acid diethylamide (LSD) ingestion during the first trimester of pregnancy.

ABNORMALITIES ASSOCIATED WITH SPECIFIC ANIMAL BREEDS

Collie eye anomaly (CEA) (Fig. 3.11)

- Although a common disorder in dogs, specimens are seldom submitted for histopathological evaluation. Only six cases are logged into the COPLOW collection
- A congenital, recessively inherited, ocular disease seen in Collies and Shetland Sheepdogs, and also in Australian Shepherds, Border Collies, Lancashire Heelers and other herding breeds. The genetics of the disorder are discussed in greater detail in Chapter 11
- Bilateral but not always symmetrical
- A wide spectrum of severity of phenotypic expression is recognized, including:
  - All cases demonstrate a regionally defined area of choroidal hypoplasia and segmental tapetal aplasia lateral to the optic disc. In isolation, this lesion has no clinically appreciable effect on vision
  - Tortuous retinal blood vessels, may be apparent, most obvious in the area of choroidal hypoplasia
  - Segmental lamina cribrosa or scleral defect (coloboma) with outward bulging or ectasia
    - Although usually adjacent to or involving the lamina cribrosa, the scleral coloboma can be slightly separate from the disc
    - Often unilateral
    - Atrophic or dysplastic neural tissue, rather than uvea, lines the staphyloma
  - Retinal detachment
    - Can be localized to the area of the optic disc, i.e. peripapillary, or complete detachment.
    - Usually unilateral
    - Usually associated with a large coloboma
    - Vitreous within the sub-retinal space probably gains access through tears in the atrophic neural tissue within the coloboma
  - Retinal dysplasia
    - Solitary or multifocal folds, or disorganized development of retinal layers with dysplasia may be seen
    - Many authors and clinicians make a point of distinguishing retinal dysplasia, which has a component of disorganization, from retinal folds, which are simply a fold or wrinkle affecting all layers
  - Hemorrhage into the posterior segment
    - The source of hemorrhage may be neovascular sprouts from the choroid; the margins of the coloboma; the dysplastic retinal foci, or traction on existing retinal vessels, however, the source is usually undetermined
  - Pre-iridal fibrovascular membranes (PIFVM)
    - This secondary abnormality may, in turn, lead to peripheral anterior synechia followed by secondary neovascular glaucoma.

Merle and white spot coat color (merle ocular dysgenesis) (Fig. 3.12)

- As with CEA, merle ocular dysgenesis is seldom submitted to the pathology laboratory, although the condition is relatively common in certain breeds, such as the Australian Shepherd, specimens are rarely submitted for evaluation. There are only three cases in the COPLOW collection
- The merle gene is a color dilution gene that lightens the coat color. Many breeds or mixed breed dogs have merle coat color variants
- A dog homozygous for the merle gene will have a lighter coat color than a heterozygous genotype. Merle-to-merle breedings are not recommended
- The merle gene does not affect white coat color or white spots
- The merle gene does affect the color of the eye, although associated abnormalities may affect eyes with brown as well as blue irides
- Dogs of any breed, or mixed breeds, with the merle color dilution (homozygous merle) and abundant white spots are at risk of congenital abnormalities in ocular development. These abnormalities include:
  - Microphthalmos
  - Iridal abnormalities
    - Iridal coloboma, iris hypoplasia
    - Asymmetric pupil size, shape, or position (dyscoria and/or corectopia)
    - Persistent pupillary membranes
  - Lens abnormalities
    - Microphakia
    - Cataract
    - Abnormal lens shape (coloboma)
    - Lens luxation/subluxation
  - Scleral defects (coloboma / staphyloma)
    - Colobomata are usually not located at the optic disc as in CEA, and are frequently equatorial in location
    - Colobomata may be very large (coloboma with cyst). The clinical picture in coloboma with cyst might be that of a fluid filled cyst making it difficult to recognize other ocular structures
  - Retinal defects
    - Retinal detachment, associated with severe dysplasia or large colobomata/staphylomas
    - Retinal dysplasia, characterized by inner retinal thickening and the formation of inner retinal rosettes
- Affected dogs are frequently also deaf.

Congenital ocular anomalies in Rocky Mountain horses (Fig. 3.13)

- An inherited complex of multiple ocular abnormalities has been reported in the Rocky Mountain horse and related breeds. In this dominantly inherited disorder, that may have incomplete penetrance, disease expression is linked to the silver dapple locus, responsible for the chocolate coat color with white or flaxen mane and tail
- Bilateral ocular involvement is seen in affected horses
- Heterozygous horses have large, translucent, temporal ciliary cysts and may also have retinal dysplasia
- Homozygous horses have a complex of abnormalities that may include the following:
  - Microphthalmos
  - Cornea globosa
    - In some affected horses the radius of curvature of the cornea appears to be shortened, leading to excessive anterior corneal curvature and the appearance of protruding eyes. These horses have abnormally deep anterior chambers

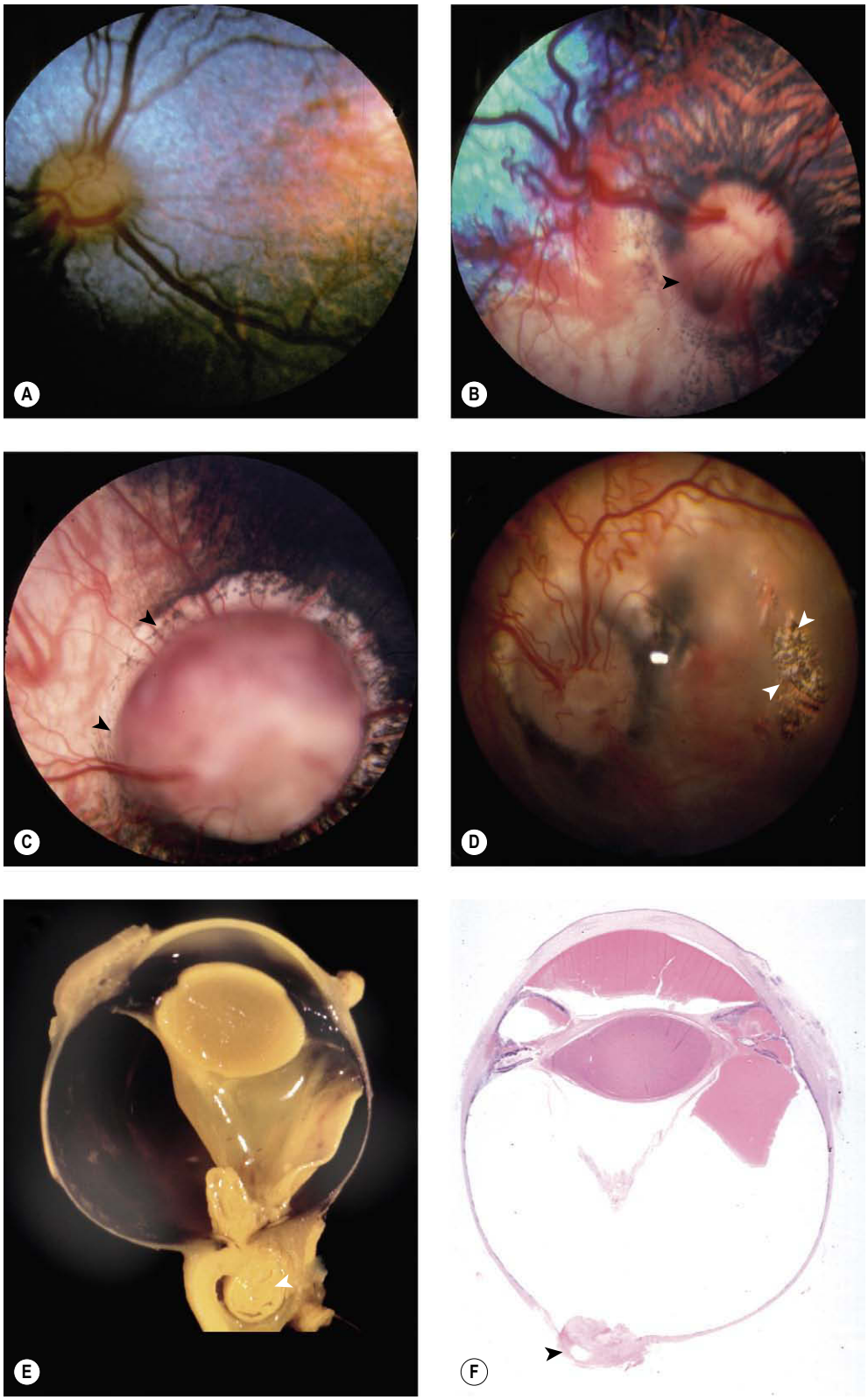


Figure 3.11 Collie eye anomaly (CEA). (A–D) Fundus photographs show various stages of Collie eye anomaly. (A) Border Collie, 3 months old: choroidal hypoplasia is present temporally in this left eye. (B) Shetland Sheepdog, 7 weeks old: this right eye has choroidal hypoplasia (below arrow) and a peripapillary coloboma at the arrow. (C) Collie, 2 years old: a large coloboma (arrow) totally surrounds the optic disc. (D) Collie, 1 year old: the retina is detached in the left eye of this subalbinotic atapetal dog. The white arrows point to a hole in the detached retina. (E) Bouin's fixed globe showing coloboma (arrow) near the optic nerve with retinal tissue entrapped within the coloboma. (F) Subgross photomicrograph of affected dog showing intraocular hemorrhage and optic nerve head coloboma (arrow).

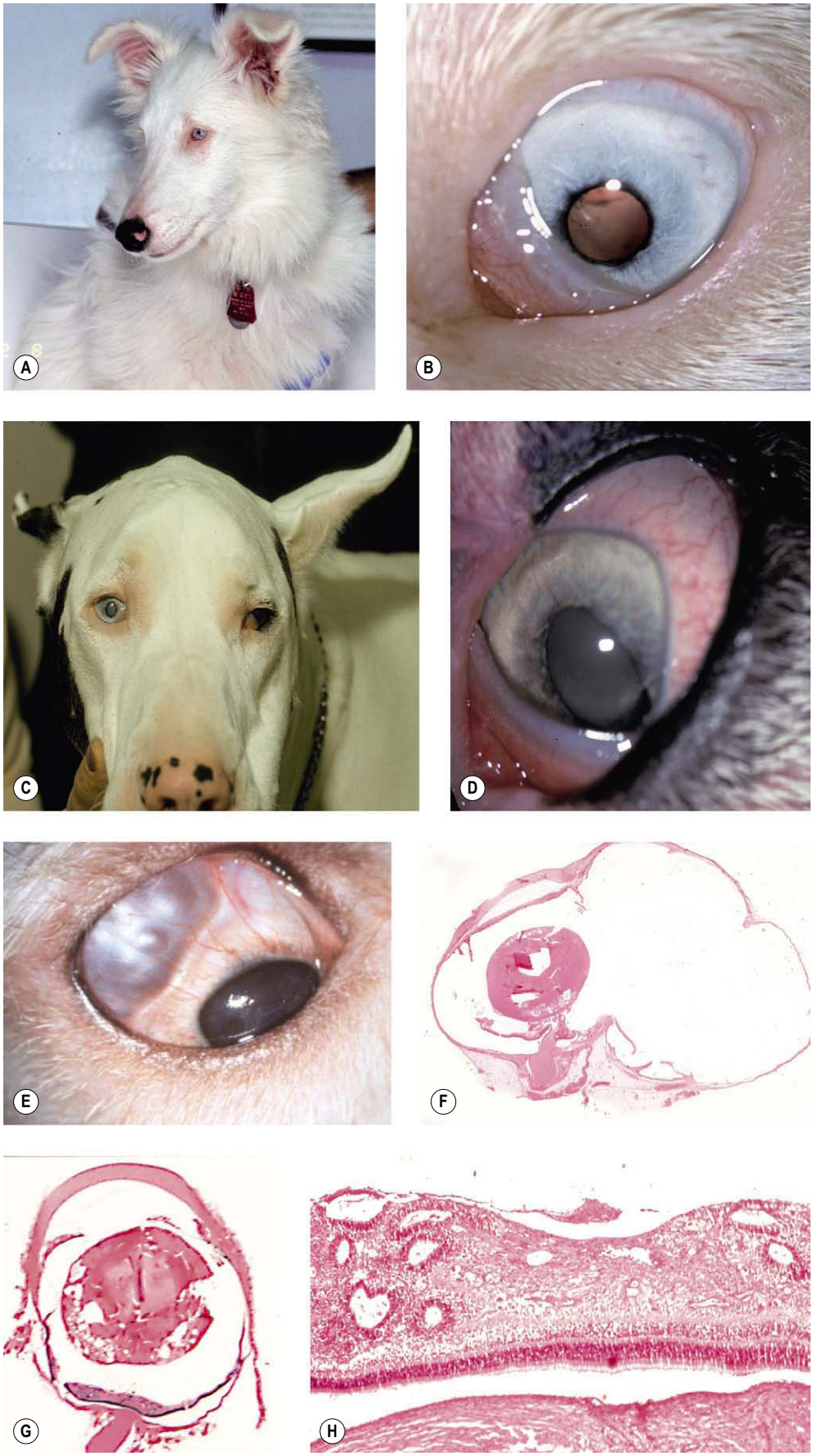


Figure 3.12 Merle ocular dysgenesis. (A) Shetland Sheepdog, 8 months old: this color dilute, deaf dog is a result of a merle-X-merle breeding. (B) The left eye of the dog in (A) shows a microphthalmic globe with multiple ocular defects including a cataract and corectopia. (C) Great Dane, 6 years old: a harlequin-X-harlequin breeding resulted in this visual dog, which had dyscoria and corectopia in both microphthalmic eyes. (D) The left eye of the dog in (C) shows the dyscoria and hypermature cataract. (E) Clinical photograph showing a sharply delineated scleral coloboma. (F) Subgross photomicrograph of the same globe as (E) showing a large segmental scleral outpouching, retinal dysplasia and microcornea. (G) Subgross photomicrograph of a microphthalmic globe with retinal dysplasia. (H) Photomicrograph of the retina from (G) showing the typical features of retinal dysplasia in merle- and white-coated dogs. There is retinal thickening and jumbled differentiation.

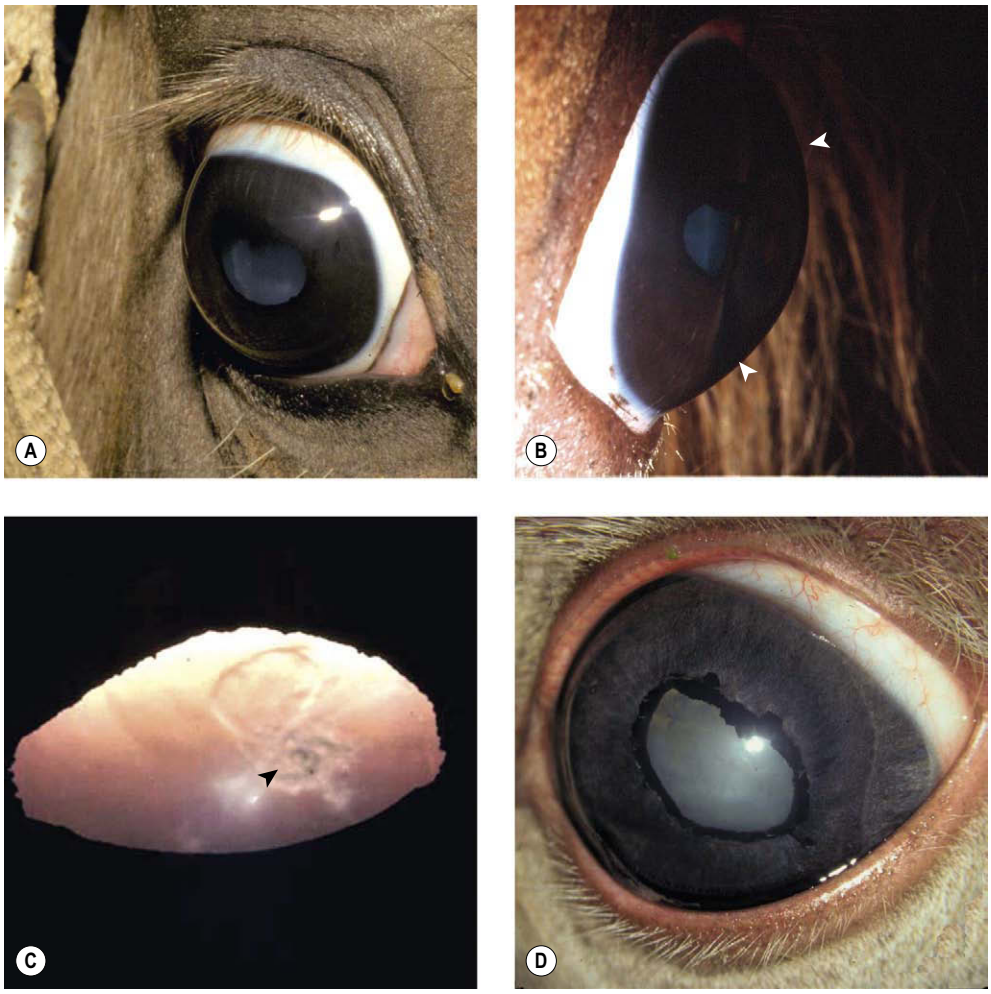


Figure 3.13 Rocky Mountain horse. (A) The right globe has a megalocornea and a diffuse cortical cataract. (B) A lateral view illustrates the increased corneal curvature (arrows) in addition to the enlarged cornea, i.e. cornea globosa. (C) A close-up photograph showing the posterior cortical opacity (arrow) and dyscoria. (D) There is dyscoria and ectropion uvea. Diffuse lens opacity can be seen through the non-mobile pupil.

- Iridal abnormalities, that include:
  - Iris hypoplasia
  - Dilator muscle hypoplasia, so that the pupils are miotic and resistant to pharmacologic mydriasis
  - Abnormal, circumferential position of the granula iridica (corpora nigra)
  - Abnormal iris surface contour
  - Irido-corneal adhesions.
  - Abnormalities of the irido-corneal drainage angle
  - Widened palpebral fissures
- Ciliary cysts
- Nuclear cataracts
- Lens subluxation.

Persistent hyperplastic primary vitreous (PHPV) and persistent hyperplastic *tunica vasculosa lentis* (PHTVL) (Fig. 3.14)

- There is a sporadic occurrence in any breed, but PHPV/PHTVL is considered to be inherited in the Doberman Pinscher and Staffordshire Bull terrier breeds.
- Specimens rarely submitted for evaluation
  - There are only 12 cases logged into the COPLOW collection
    - Three of the 12 are in Doberman Pinschers
- The primary vitreous, including the hyaloid vasculature and the *tunica vasculosa lentis*, provide a blood supply to the fetal lens, and in dogs completely regress shortly after birth
- In dogs with PHPV/PHTVL, the first observable abnormalities are seen about halfway through gestation (30–33 days), when the hyaloid vasculature and *tunica vasculosa lentis* appear over-developed relative to normal, and a retro-lental membrane may first be recognized
  - The abnormalities are usually centered on the vitreous but there can be variable involvement of the whole retro-lental vascular system, and anterior tunica vasculosa lentis
  - In moderate and severe cases, tissue may be recognized that would not be identified in the normal primary vitreous
    - Cartilage
    - Pigmented tissue
    - Nests of glial tissue
  - Posterior lenticonus, cataract and posterior lens capsule defect is often seen
  - Intralenticular hemorrhage is sometimes seen
    - Although hemorrhage within the lens is a good morphologic marker for a congenital abnormality of the fetal hyaloid vasculature, it does not discriminate between PHPV, PHTVL, and persistent hyaloid artery

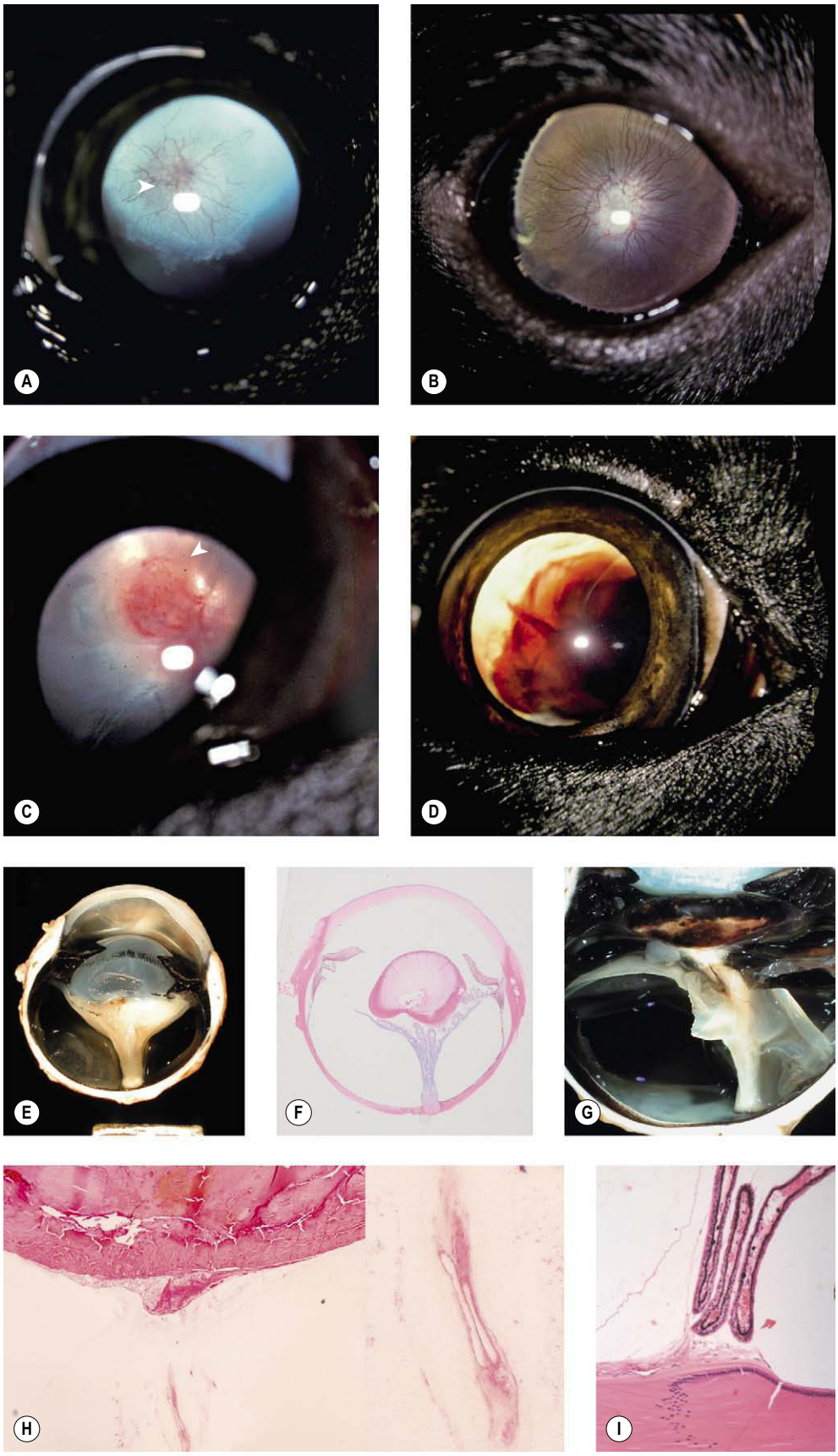


Figure 3.14 Persistent hyperplastic primary vitreous and persistent hyperplastic *tunica vasculosa lentis* (PHPV/PHTVL). (A) Labrador Retriever, 1.5 years old: the arrow points to the network of fine blood vessels on the posterior lens capsule. A posterior axial cataract resulted from the PHPV. (B) Dachshund, 7 months old: fine vessels can be seen extending to the equator of the posterior lens in this bilateral condition. (C) Doberman Pinscher, 6 months old: the PHTVL resulted in an axial vascular area surrounded by a retrolental fibrovascular plaque (arrow). (D) German Pinscher, 1.5 years old: through the dilated pupil, the severe bleeding into the lens can be seen with PHPV. (E) Gross photograph showing PHPV and retinal detachment. (F) Subgross photomicrograph of the same globe as (E). (G) Gross photograph of retinal detachment and PHPV. (H) Photomicrograph showing a PHPV on the posterior pole of the lens (the insert is a higher magnification of the vessel in the mid-vitreous). (I) Photomicrograph of vascular structures extending from the pars plicata to the lens capsule.

- Retinal detachment may be seen in severe cases
  - Retinal detachment can lead to pre-iridal fibrovascular membrane, and contribute to neovascular glaucoma or anterior segment hemorrhage
  - Retinal dysplasia may accompany PHPV, as has been reported in the Miniature Schnauzer as a recessively inherited condition, and as a familial trait in the Bouvier des Flandres.

Retinal dysplasias (Fig. 3.15)

- An important hereditary abnormality in dogs, retinal dysplasia, is seldom encountered as a genetic disease in other species
- Globes with retinal dysplasia in isolation are almost never submitted to the diagnostic ocular pathology laboratory
  - The only cases identified in the COPLOW collection are those in which retinal dysplasia accompanies other abnormalities of serious consequence to ocular health and/or vision
  - Because so few cases are seen in a pathology collection, and because the only cases seen are in a special context, a diagnostic ocular pathologist has little beyond generalities to add to the understanding of these developmental disorders
- Definition: the disorganized development of retinal tissue
  - Solitary or multi-focal disease
- Many breeds of dog are affected, and the reader is referred to the most recent edition of *Ocular Disorders Presumed To Be Inherited in Purebred Dogs*, with regular updates available from the Canine Eye Registration Foundation (CERF)
- Retinal dysplasia is characterized funduscopically as well-demarcated, linear, curvilinear or larger, geographic foci, that may be raised or wrinkled, and may be accompanied by pigment disturbance or evidence of associated retinal degeneration. In some cases, funduscopic lesions may not be readily identifiable until secondary degenerative changes become apparent
  - Linear lesions are generally considered to represent 'folds', which some consider as a distinct entity not qualified to be considered as dysplasia, in the absence of significant tissue disorganization
    - Some feel that simple retinal folds in puppies are likely to disappear with the subsequent maturation and physical enlargement of the globe
  - Geographic lesions are likely to include retinal lesions beyond just folding
    - Rosettes
    - Thickening or thinning
    - Jumbling of the retinal layers
    - Focal retinal detachment, or local changes in the RPE, with accompanying retinal degeneration.

The vitreoretinopathies – vitreoretinal dysplasia (Figs 3.16, 3.17)

By virtue of the blinding effect of retinal detachment, intraocular hemorrhage and the risk of neovascular glaucoma, vitreoretinopathy is more often seen in the pathology laboratory than retinal dysplasia alone, with 58 cases logged into the COPLOW collection.

- Congenital, inherited retinal detachment/non-attachment is recognized in Bedlington and Sealyham terriers. For a comprehensive breakdown of the breeds affected by vitreoretinal dysplasia, the reader is referred to the most recent edition of *Ocular Disorders Presumed To Be Inherited in Purebred Dogs*, with regular updates available from the Canine Eye Registration Foundation (CERF)
- This diagnosis is made when there is abnormal development of both the vitreous and the retina. Because the two tissues are so intimately connected, disease of one impacts the health of the other
- The vitreous body is formed by scant spindle cells, a connection to the retina by attachment to the inner limiting membrane (a basal lamina secreted by retinal Müller cells), and hyaluronic acid secreted by the ciliary epithelium
- The vitreous changes seen include:
  - Areas of liquid vitreous which can only be recognized on gross examination, prior to embedding
  - Areas of more dense, organized, or 'solid' vitreous
    - These areas create traction on the retina and can be associated with subsequent retinal detachment
    - Traction on the retina from the abnormal vitreous can be associated with broad peripheral retinal disinsertion (tearing) or with more localized peripheral retinal tears. Retinoschisis is also sometimes recognized. Abnormal cellular membranes on the inner retinal surface are often seen in vitreoretinopathies
    - Areas of solid vitreous can be best seen with an Alcian blue stain, and they often stain positively for collagen with a trichrome stain
- Retinal detachment, and resulting retinal hypoxia, leads to the release of vasoproliferative cytokines, particularly vascular endothelial growth factor (VEGF), which stimulate pre-iridal fibrovascular membrane (PIFVM) formation. This, in turn, leads to peripheral anterior synechiae and neovascular glaucoma and/or hemophthalmos.
- Vitreoretinopathy of the Shih Tzu dog
  - Vitreoretinopathy in this breed is often not recognized until neovascular glaucoma is seen secondary to retinal detachment
  - There are 30 cases of Shih Tzu vitreoretinopathy in the COPLOW collection (Figs 3.16, 3.17)
    - In this breed, the disease is usually presented in middle-aged dogs, rather than very young dogs
    - The detection of vitreous changes often requires either careful attention to the gross morphology at the time of globe trimming, or an Alcian blue stain
    - The vitreous is usually liquid in much of the posterior segment but condensed at the inner retinal surface
    - Retinoschisis is often seen in the detached retina
  - There is traction and peripheral retinal tearing leading to local or extensive retinal detachment (rhegmatogenous retinal detachment and giant retinal tears)
  - The formation of peripheral retinal tears associated with vitreous degeneration and traction may represent a good comparative model for the study of pathogenesis, treatment and prevention of peripheral rhegmatogenous retinal detachment in humans
  - By the time affected globes are removed, they frequently have neovascular glaucoma or intraocular hemorrhage associated with the formation of pre-iridal fibrovascular membranes and peripheral anterior synechiae
  - Although these cases might not find their way to the pathologist until complete retinal detachment and disinsertion leads to neovascular glaucoma, they are regularly presented to veterinary ophthalmologists. In recent years surgical re-attachment of the retina has become an option.

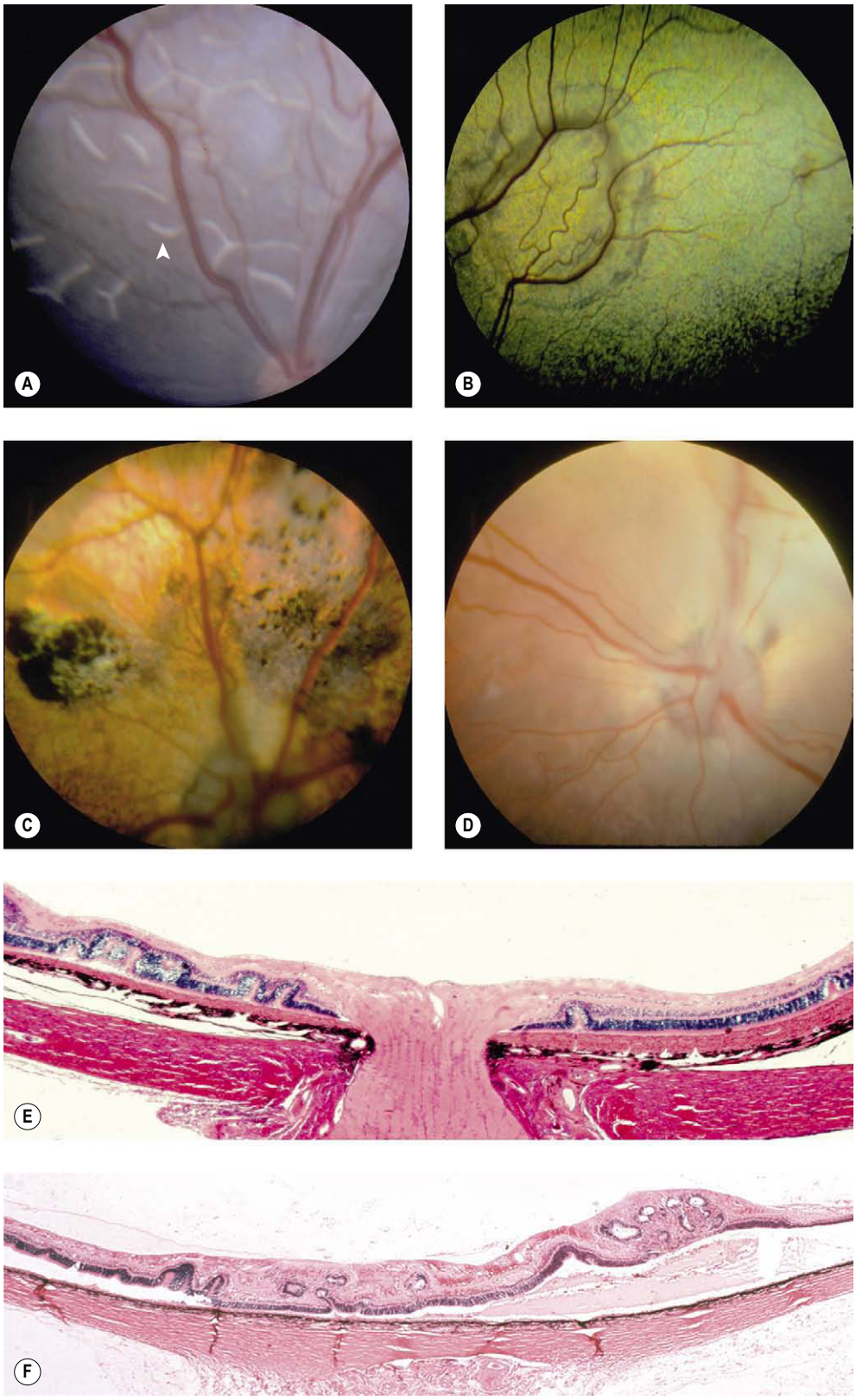


Figure 3.15 Retinal dysplasia. (A) Cavalier King Charles Spaniel, 8 weeks old: multiple linear retinal folds (arrow) are seen in this immature fundus. (B) Golden Retriever, 2 years old: the large geographic tapetal lesion is discernible due to the change in tapetal coloration. (C) English Springer Spaniel, 18 months old: large areas of abnormal pigmentation and tapetal hyperreflectivity are indicative of severe geographic retinal dysplasia. (D) English Springer Spaniel, 2.5 years old: a complete retinal detachment obscures the fine detail of the underlying tapetum and non-tapetal pigmented fundus. (E,F) Photomicrographs show multifocal retinal dysplasia, characterized by retinal folds and disorganization of the retinal layers.

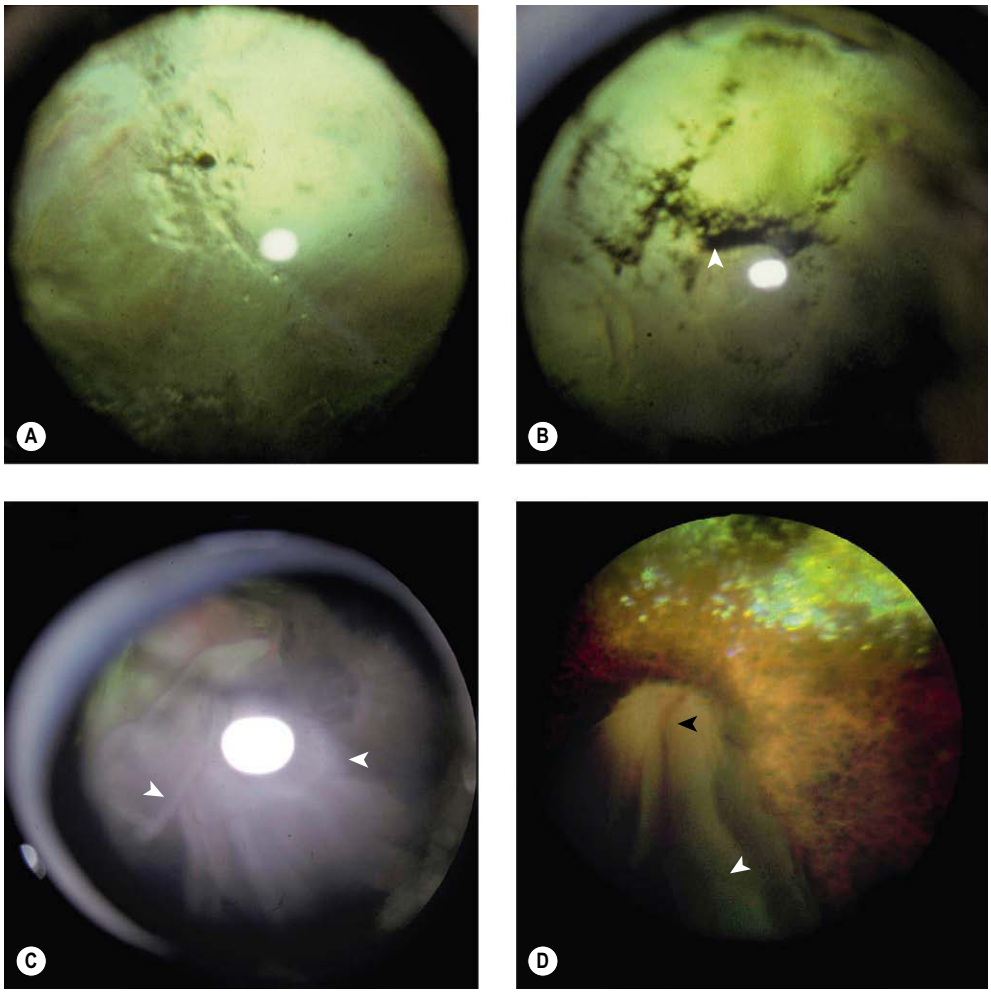


Figure 3.16 Vitreoretinopathy in the Shih Tzu, clinical. (A) Shih Tzu, 6 years old: the vitreous degeneration can be seen by retroillumination. (B) Shih Tzu, 4.5 years old: total retinal detachment resulted in tapetal hyperreflectivity and vitreous hemorrhage (arrow). (C) Shih Tzu, 4.5 years old: the gray discoloration (between arrows) represents the detached retina. (D) Shih Tzu, 15 months old: the optic disc can be seen at the black arrow with the veil-like detached retina inferior (white arrow).

Oculo-skeletal dysplasia syndrome (Figs 3.18, 3.19)

There are seven cases of oculo-skeletal dysplasia in the COPLOW collection.

- Seen in Labrador retrievers and Samoyeds
- Autosomal dominant inheritance with incomplete penetrance has been postulated
  - Heterozygous animals usually have mild retinal dysplasia
  - Homozygous animals have skeletal changes and mild to severe retinal dysplasia
    - There is a correlation between the phenotypic severity of the ocular and the skeletal manifestations of the disease. Animals with severely affected eyes generally have pronounced chondrodysplastic dwarfism
    - Skeletal abnormalities affect the growth plate and result in shortened and hypoplastic chondrocyte columns
    - Ocular changes
      - The least affected eyes have focal or multifocal retinal dysplasia and prominent vitreous strands
      - Mildly affected globes have focal retinal detachment and a combination of liquefied areas in the vitreous and thick vitreous strands attached to the inner retina
      - Severely affected globes have complete retinal detachment, with disinsertion and wrinkling of the peripheral retina inward towards the optic disc
    - Decreased amounts of type II collagen in the vitreous of affected Labrador retrievers. Type II collagen is a component of the growth plate as well as normal vitreous
    - The end-stage ocular disease occurs when the retinal detachment leads to pre-iridal fibrovascular membranes and subsequent neovascular glaucoma, and intraocular hemorrhage.

Congenital cataract (lens opacity) and other congenital abnormalities of the lens

Normal lens structure (Fig. 3.20) (see Ch. 10)

- Nucleus and cortex
- Lens capsule (anterior and posterior)
- Lens epithelium
- Lens fibers
- Anterior and posterior sutures.

Congenital lens abnormalities other than cataract

Aphakia

- Primary aphakia, no lens anlage developed
  - This extremely rare abnormality occurs in combination with other anterior segment abnormalities (see anterior segment dysgenesis) and/or microphthalmos

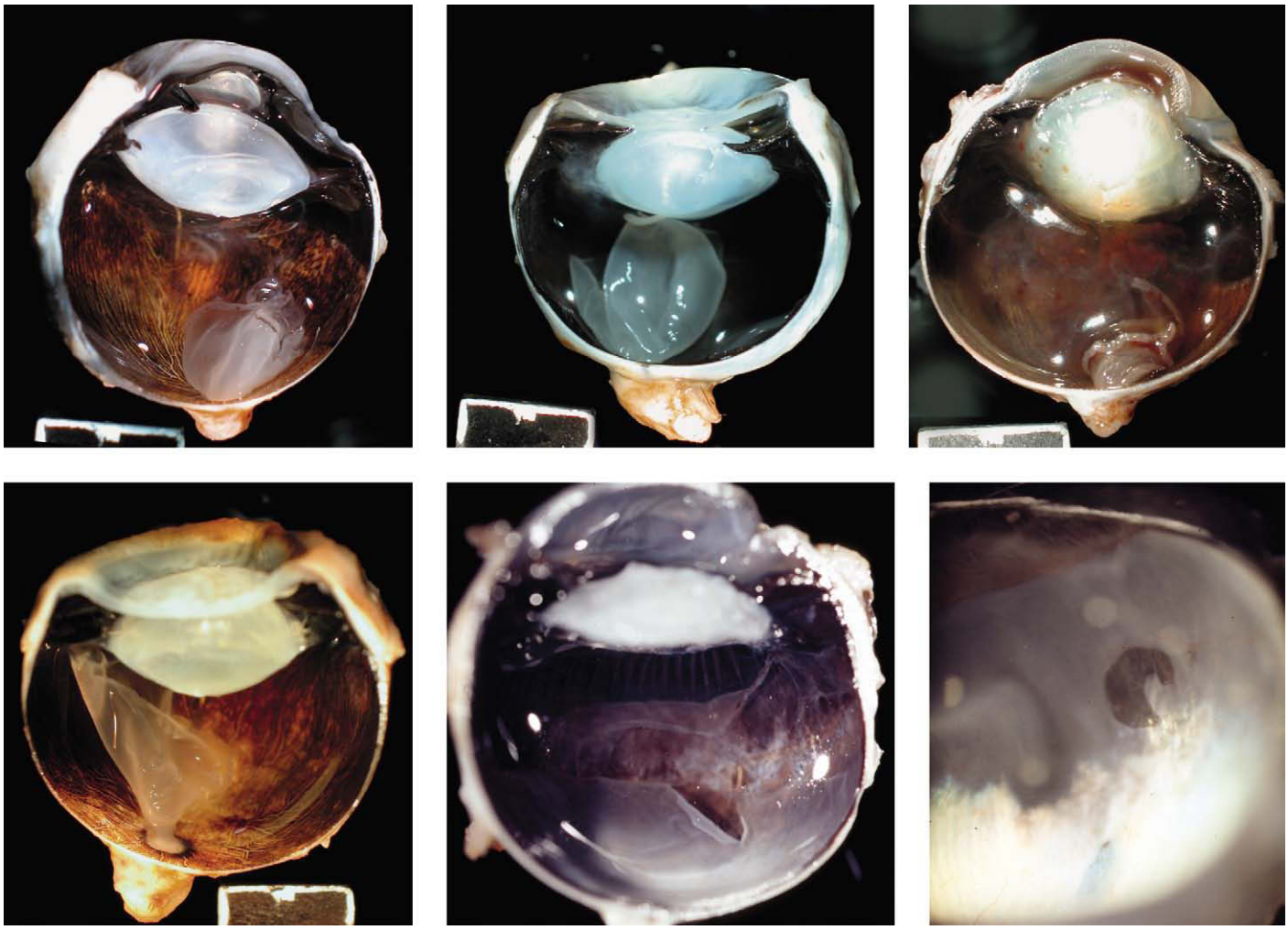


Figure 3.17 Vitreoretinopathy in the Shih Tzu, gross pathology. Six gross photographs of Shih Tzu globes with vitreoretinopathy and giant retinal tears.

- Secondary aphakia, early lens extrusion, resorption or destruction
  - Early life trauma or inflammation
  - Wrinkled remnants of lens capsule may be seen if the tissue is sectioned in the appropriate plane.

Lens coloboma and microphakia (Fig. 3.21)

- These conditions may represent abnormalities of the zonular suspensory apparatus, rather than primary abnormalities in lens development
- Often associated with other congenital abnormalities such as uveal colobomata, retinal detachment, anterior segment dysgenesis and PHPV/PHTVL.

Posterior lenticonus and lentiglobus (Fig. 3.22)

- Posterior protrusion and increased curvature of the posterior pole of the lens
- Seen as a breed-related problem in Cavalier King Charles Spaniels but seen sporadically in many breeds of dog and in many species, and is often associated with cataract
- Clinically the cataract is in focus on the posterior pole of the lens, which has a globular appearance
- Histologically there is thinning, or rupture, of the posterior capsule and a posterior bulging of the posterior polar lens cortex
- Often seen in combination with persistent hyaloid artery or PHPV/PHTVL.

Development of anterior lens features on the posterior pole

- This unusual phenomenon happens when other features, such as PHPV/PHTVL or dysplastic retinal tissue, make broad contact with the posterior pole of the lens, and the posterior lens differentiates like the anterior pole
- The lens epithelium wraps around to the posterior pole (posterior migration)
- The posterior capsule becomes thick
- The epithelium, displaced to the posterior pole, forms a second posterior nuclear bow.

Congenital cataract (Fig. 3.23)

- Congenital cataract should imply that the cataract is present at birth. However, animals are seldom evaluated at birth, therefore

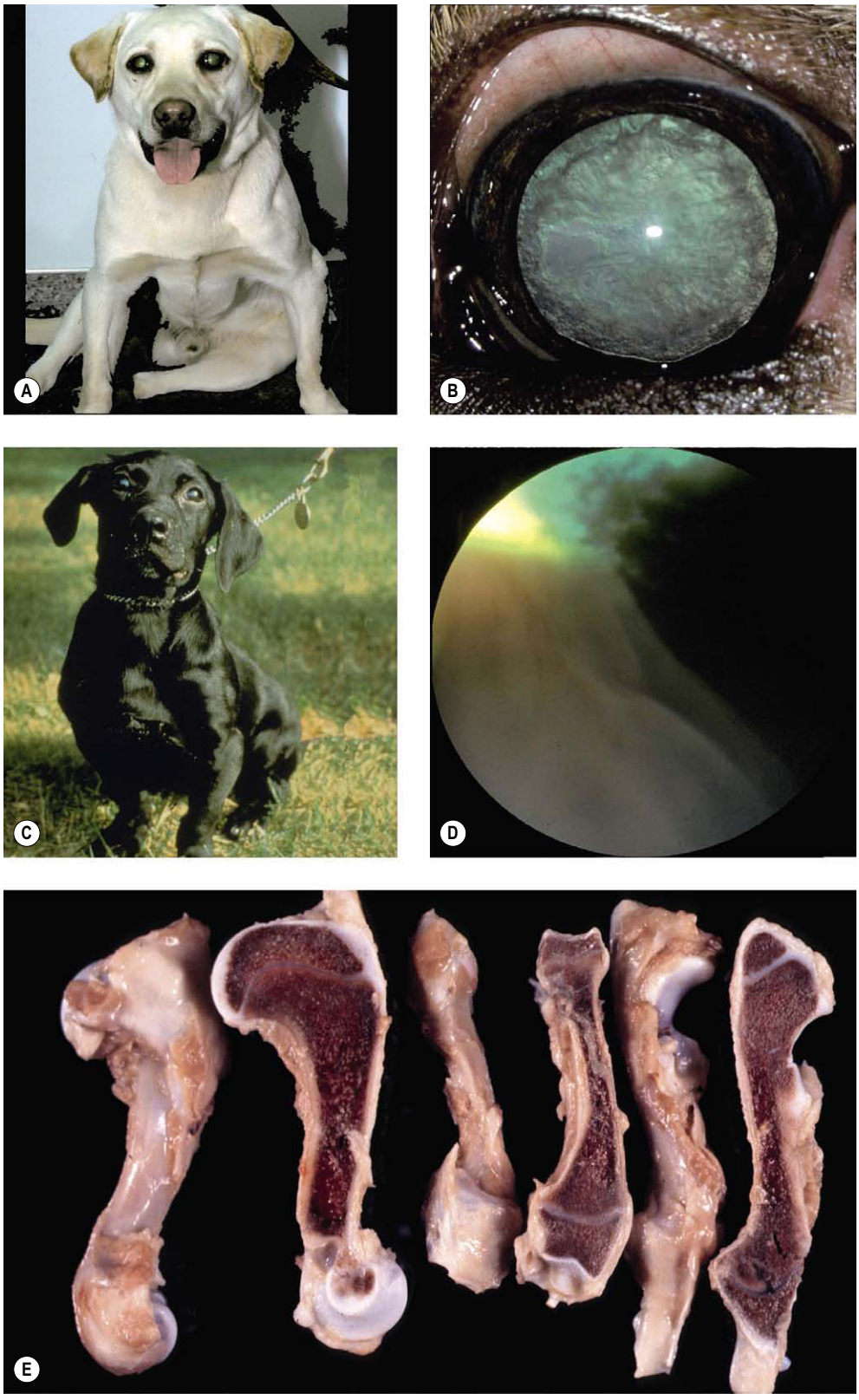


Figure 3.18 Oculo-skeletal dysplasia syndrome. (A) Labrador Retriever, 10 months old: showing shortened and deformed long bones. (B) Clinical photograph of the left eye of the dog depicted in (A), with a diffuse cortical cataract and retinal detachment; condition was bilateral. (C) Labrador Retriever, 5 years old: the short stature is associated with varus elbow deformities and valgus deformities at the carpi. (D) Labrador Retriever, 11 months old: the totally detached and disinserted retina is seen as a gray veil hanging from the optic disc. (E) Sectioned pectoral limb bones show foreshortened bone growth.

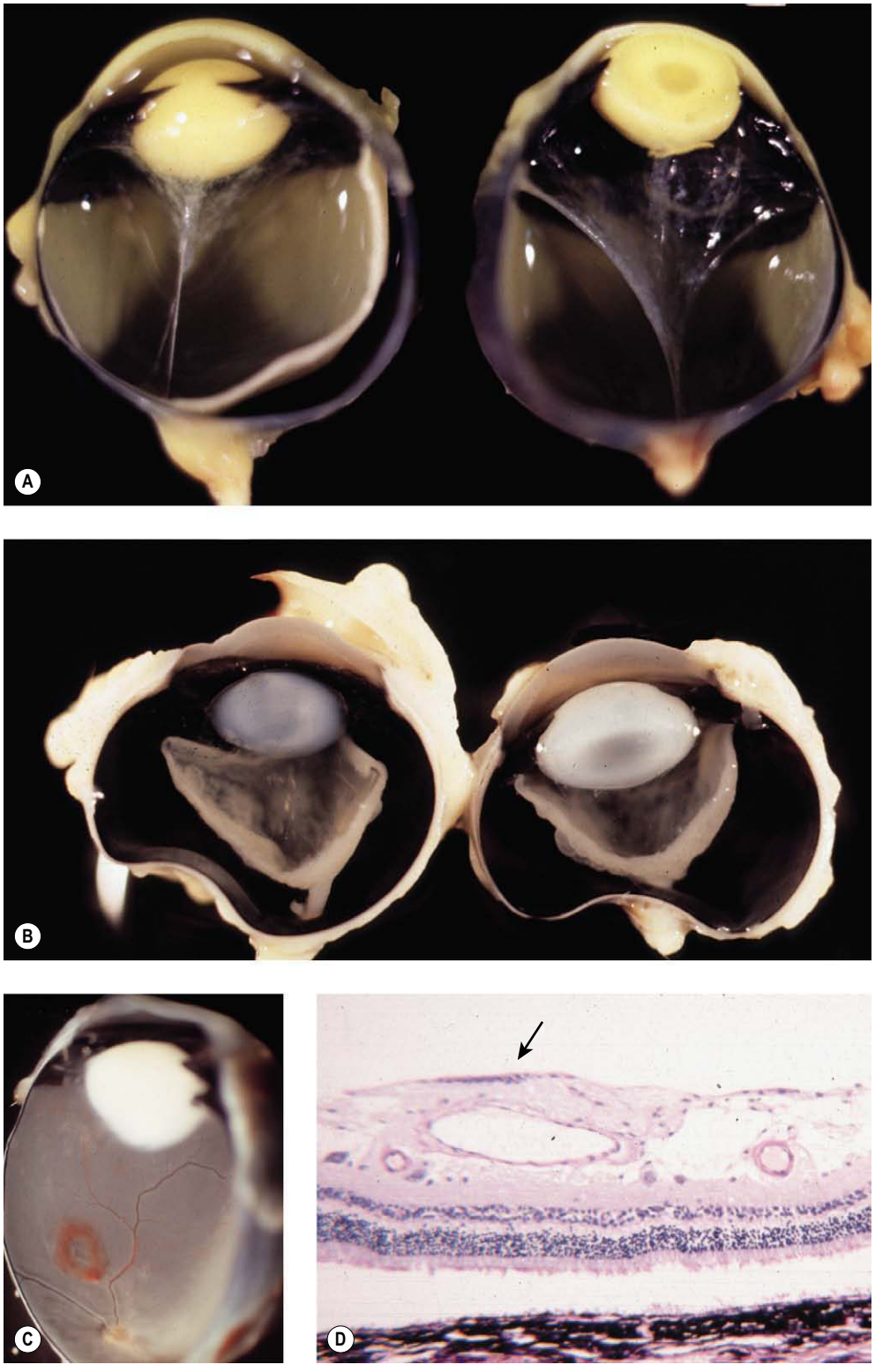


Figure 3.19 Oculo-skeletal dysplasia syndrome, ocular pathology. (A) Gross photograph of both globes from a Labrador Retriever with oculo-skeletal dysplasia showing strands in the vitreous body. (B) Both globes from another dog have complete retinal detachment and giant retinal tears, accompanied by inward scrolling of the free ends of the peripheral retina. (C) Gross photograph showing a vascularized inner retinal membrane from an affected dog. (D) Photomicrograph of the retina showing a cellular membrane on the inner retinal surface (arrow).

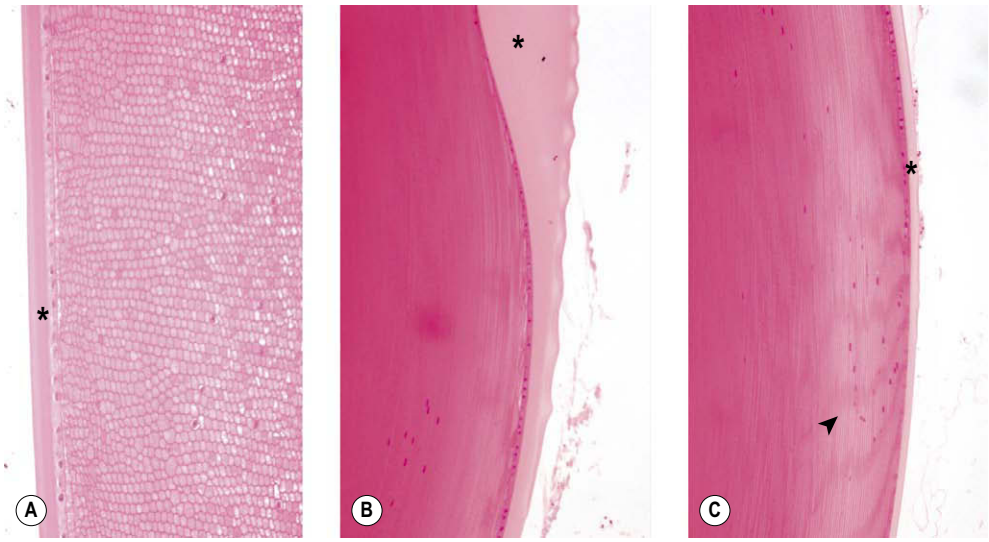


Figure 3.20 The normal lens. In these three photomicrographs of the normal lens, the lens capsule is indicated with an asterisk (*). (A) The anterior pole. (B) The anterior pole midway to the equator. The lens capsule gets thinner (*). (C) The nuclear bow (*) at the equator. The arrow points to a nucleus in the nuclear bow.

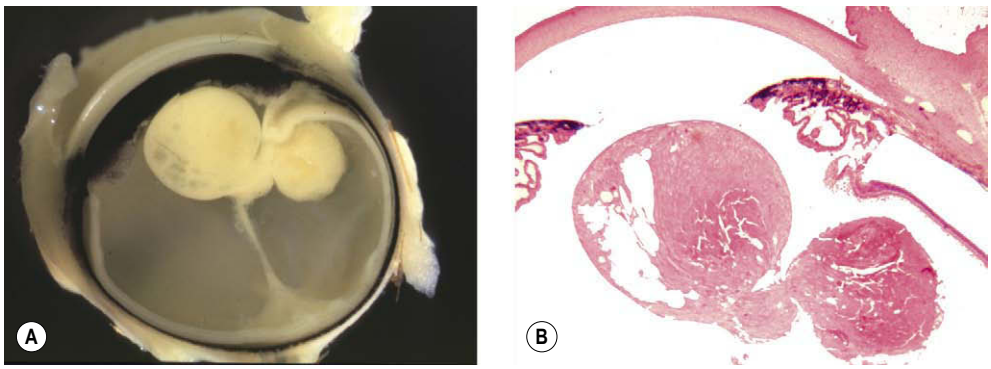


Figure 3.21 Congenital lens coloboma in a ferret. (A) Gross photograph of a bilobed lens in a ferret. (B) Subgross photomicrograph of the globe.

the condition is defined by the age of first appearance, and because of that, the definition may differ between authors (Fig. 3.23)

- Congenital cataract, in isolation, is very unlikely to be seen in a pathology laboratory because the eye is not likely to be painful, the health of the animal is not likely to be adversely affected, and there is an effective surgical therapy
- Congenital cataract is often associated with more complex syndromes involving other ocular abnormalities, including microphthalmos, PHPV/PHTVL, PPM and/or anterior segment dysgenesis
- Although inherited forms of congenital cataract are recognized in a wide range of species, congenital cataract often occurs sporadically, or as a result of maternal exposure to toxins, infection, or other *in utero* insult during lens development
- Congenital cataract, as any cataract, can affect the lens in a variety of morphological patterns
  - Lesions involving the lens capsule and epithelium
    - Disorganization of the lens epithelium
    - Posterior migration of lens epithelial cells
    - Duplication of lens capsule
  - Lesions involving the relative formation of the nucleus and cortex
    - Nuclear cataract is most likely to be encountered in isolation
  - Cortical cataract.

Hereditary cataracts

- Morphologically, most breed-related cataracts are cortical cataracts that are not present at birth. Hereditary cataract is discussed further in Chapter 10.

Goniodysgenesis and other anterior segment dysgenesis syndromes (Figs 3.24, 3.25)

Goniodysgenesis is also known as pectinate ligament dysplasia, and mesodermal dysgenesis (Figs 3.24, 3.25). There are 1100 cases of dogs with a diagnosis of goniodysgenesis in the COPLOW collection.

- This morphologic variant is an important risk factor in development of 'primary glaucoma' of dogs; the glaucoma syndrome will be discussed in more detail in Chapter 13
- Morphologic features of goniodysgenesis
  - Gross appearance as described by gonioscopy *in vivo*, or by direct inspection with a dissecting microscope during gross evaluation
    - The normal pattern of the primary pectinate ligament is replaced focally or in broad sheets by a solid band of uveal tissue, that may be fenestrated to a variable degree
  - Microscopic appearance of goniodysgenesis in the normotensive eye

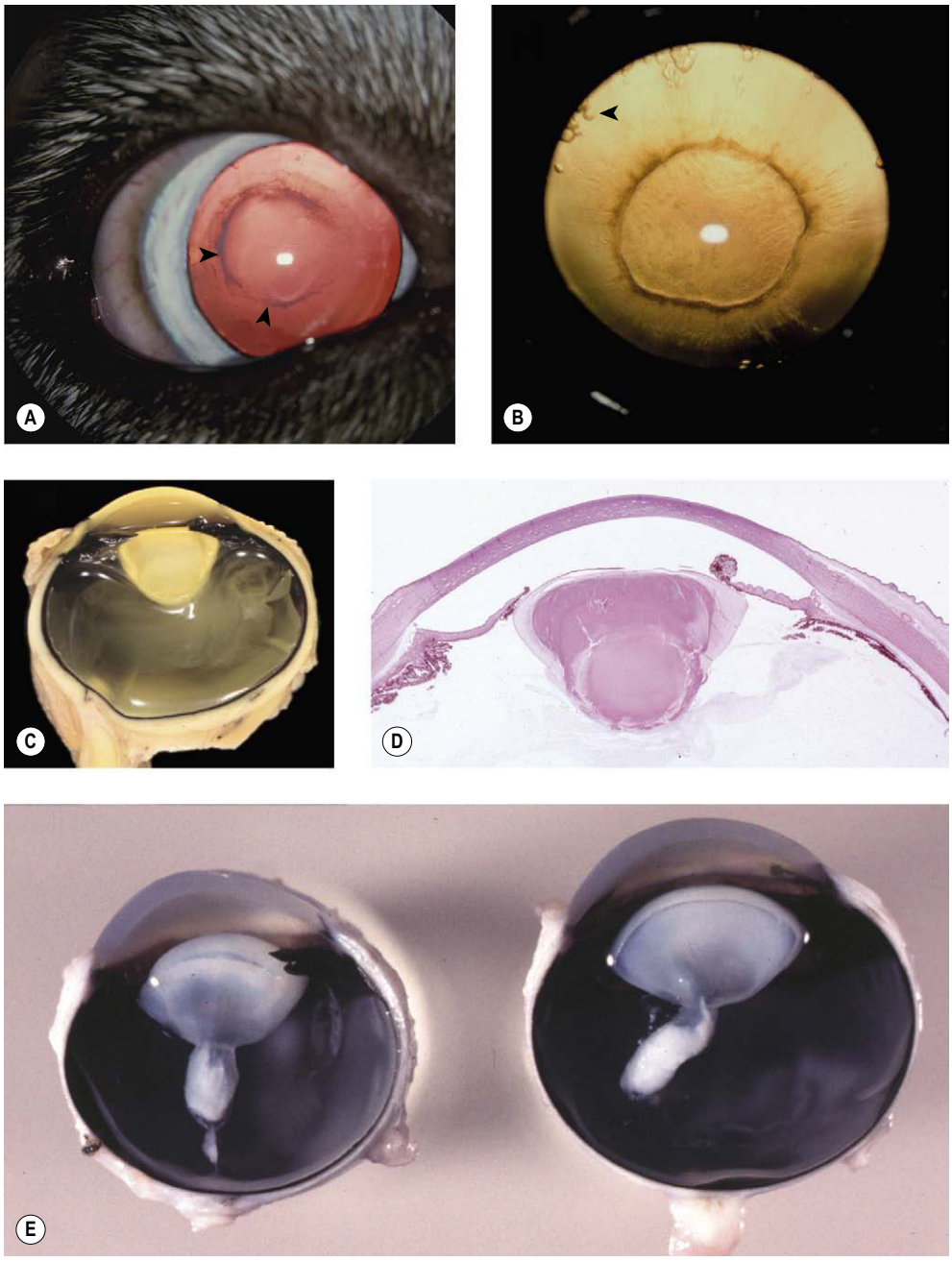


Figure 3.22 Posterior lenticonus. (A) Siberian Husky, 6 months old: arrows outline the area of posterior protrusion of the lens. (B) Golden Retriever, 1 year old: the dark circle outlines an area of lenticonus with additional cortical opacities radiating toward the lens equator. The arrow points to the equatorial water cleft. (C) Gross photograph of an equine globe with lenticonus. (D) Photomicrograph of the same globe as (C). (E) Both globes from a Cavalier King Charles Spaniel show the abnormal tubular extension from the posterior pole of the lens blending into hyaloid arterial remnants.

  - The hallmark feature is a solid sheet of iris-like tissue extending from the base of the iris to the termination of Descemet's membrane
    - Classically this membrane should have both pigment cells and dense collagen, similar to the canine iris
    - The termination of Descemet's membrane is distorted by branching, bulging, or both
    - In the normotensive eye, the ciliary cleft is open and the corneoscleral trabecular meshwork is readily identifiable.

Peter's anomaly and persistent pupillary membranes (Figs 3.26, 3.27)

There are 10 cases of Peter's anomaly in the COPLOW collection, six in dogs and four in cats.

- The defining feature of Peter's anomaly is a congenital defect in the posterior cornea, resulting from failure of normal kerato-lenticular separation
  - Segmental defect in Descemet's membrane and endothelium (required abnormality)
  - Clinically, there is a segmental corneal opacity
  - Attachment of uveal tissue to the posterior surface of the cornea
    - Pigmented tissue
    - Vascular tissue
    - Uveal strands stretching from the iris to the cornea focally or multifocally
  - Usually not associated with congenital glaucoma
- The defining feature of persistent pupillary membranes is vascularized uveal strands or membranes stretched across the

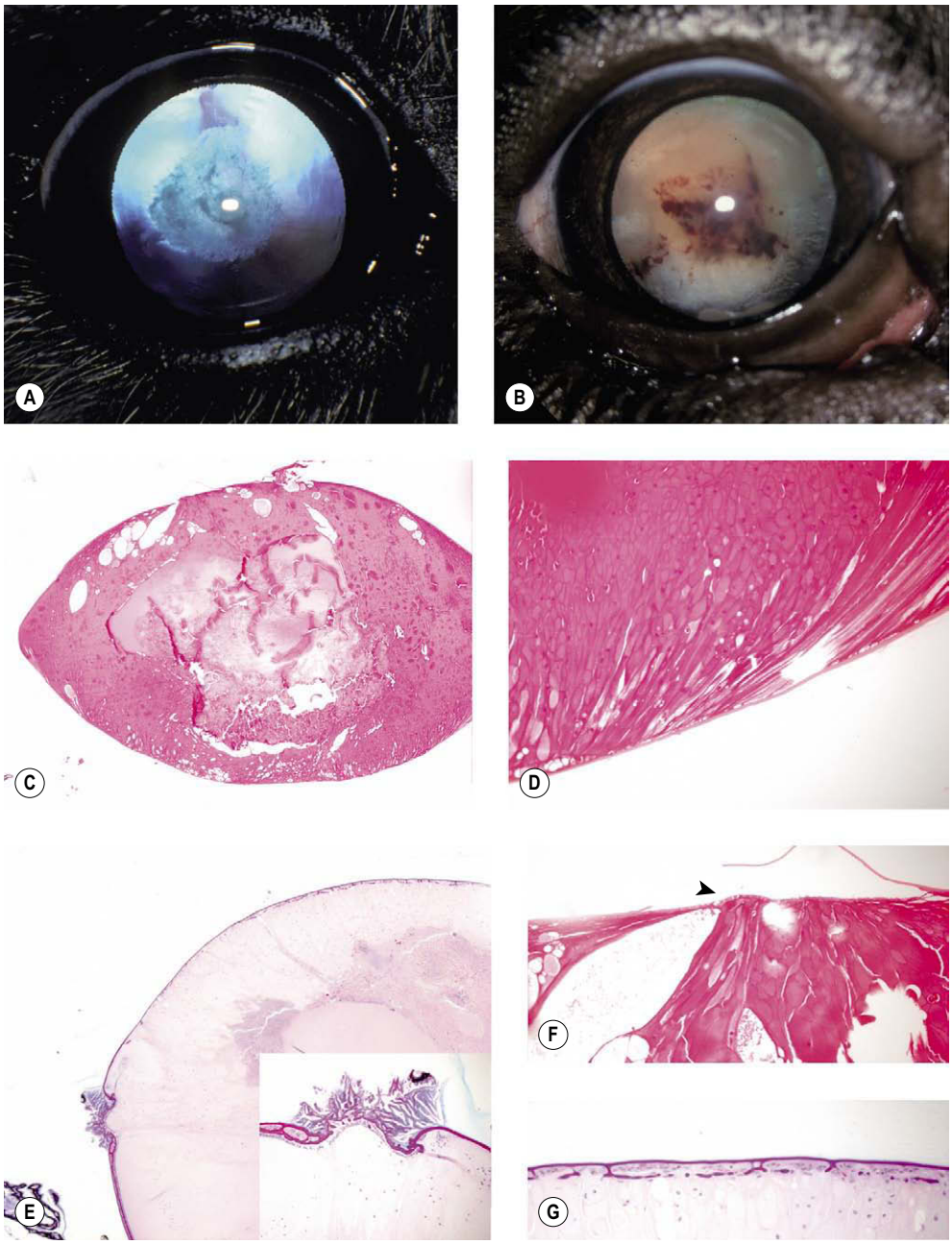


Figure 3.23 Congenital cataracts. (A) Miniature Schnauzer, 1 year old: the central opacity seen is a nuclear cataract. (B) Bloodhound, 5 months old: the PHPV resulted in a diffuse cortical opacity with hemorrhage into the posterior cortex. (C) Subgross photomicrograph of congenital cataract. (D) Photomicrograph of the same lens as (C), showing cataract in the posterior pole and nucleus. (E) Photomicrograph showing congenital cataract and focal lens capsular wrinkling highlighted in the inset (PAS stain). (F) Photomicrograph showing severe lens fiber degeneration at the posterior suture (arrow) of a congenital cataract. (G) Photomicrograph of the anterior capsule, epithelium and redundant capsular deposits in a congenital canine cataract (PAS stain).

pupil, extending from one side of the iris to the other, or to the anterior pole of the lens.

Congenital failure in the formation of the anterior segment, anterior segment dysplasia or dysgenesis (Fig. 3.28)

- The defining feature is broad anterior adhesion of iris, or iris remnants, to the posterior cornea in association with abnormalities in Descemet's membrane and endothelium. The space that normally represents the anterior chamber may be narrow or non-existent
- Lens may make contact with cornea within a defect in Descemet's membrane
  - This represents a failure of kerato-lenticular separation at the time of formation of the lens vesicle from the surface ectoderm
- May be associated with congenital glaucoma and buphthalmos, or with microphthalmos
- This diagnosis should be made with care. The diagnosis of congenital disease needs to be carefully differentiated from early life trauma with acquired anterior segment collapse. The presence of other features which cannot be explained by acquired disease, particularly trauma will aid in making the diagnosis of congenital disease

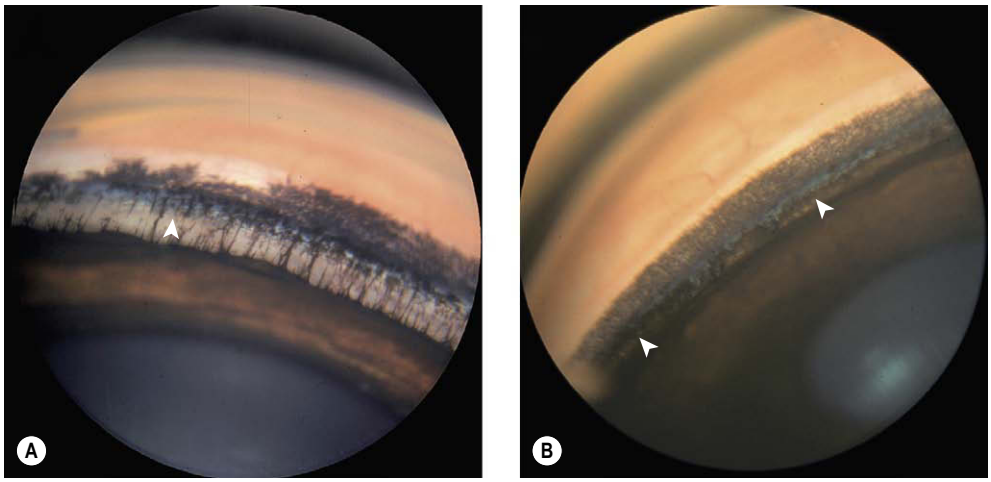
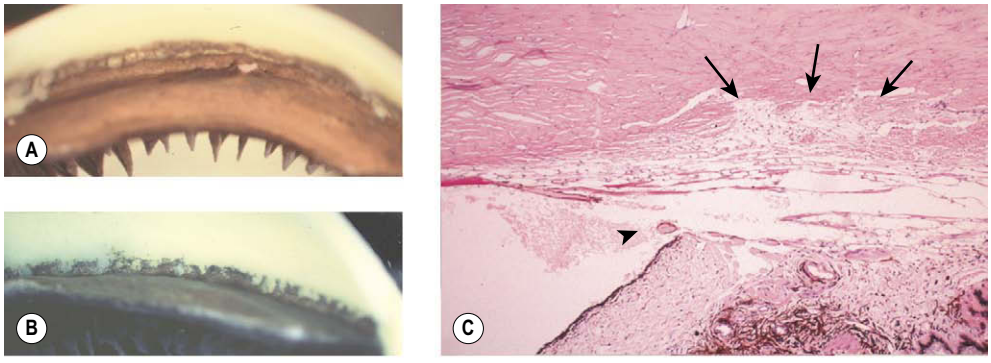


Figure 3.24 Canine goniodysgenesis, gonioscopy. (A) Beagle, 2 years old: this clinical image is of a normal irido-corneal angle. The ciliary cleft can be seen between the pectinate ligaments (arrow). (B) Basset Hound, 2 years old: this image shows goniodysgenesis in a normotensive eye. A broad band of tissue (arrows) obscures the ciliary cleft.



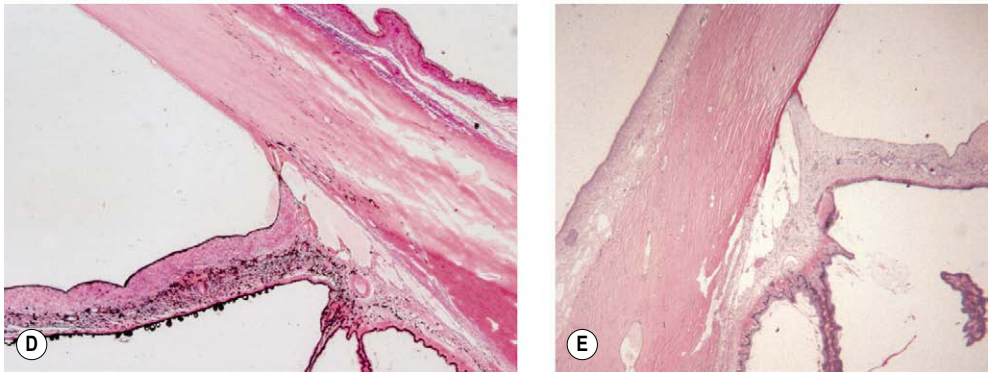


Figure 3.25 Goniodysgenesis, pathology. (A,B) Magnified gross photographs of canine iridocorneal angle show features of severe (A) and mild (B) goniodysgenesis. (C) Photomicrograph of a normal canine irido-corneal angle showing a primary pectinate (arrowhead) and the corneoscleral trabecular meshwork (small arrows). (D,E) Photomicrographs show canine goniodysgenesis in two normotensive dogs.

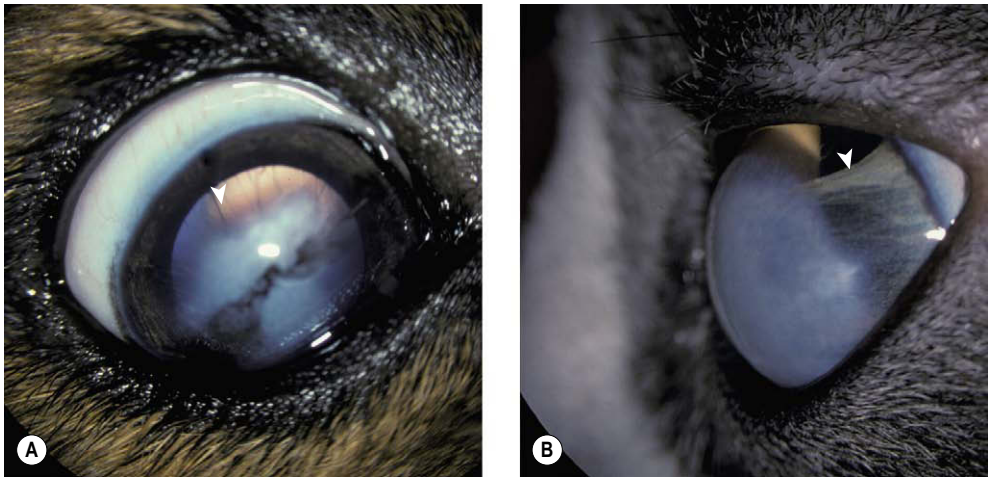


Figure 3.26 Peter's anomaly, clinical. (A) Chow Chow, 8 weeks old: fine persistent pupillary membranes from the iris to the cornea (arrow) associated with a diffuse corneal edema. (B) DSH, 2 years old: thick bands of uveal tissue (arrow) led to severe edema and keratoconus.

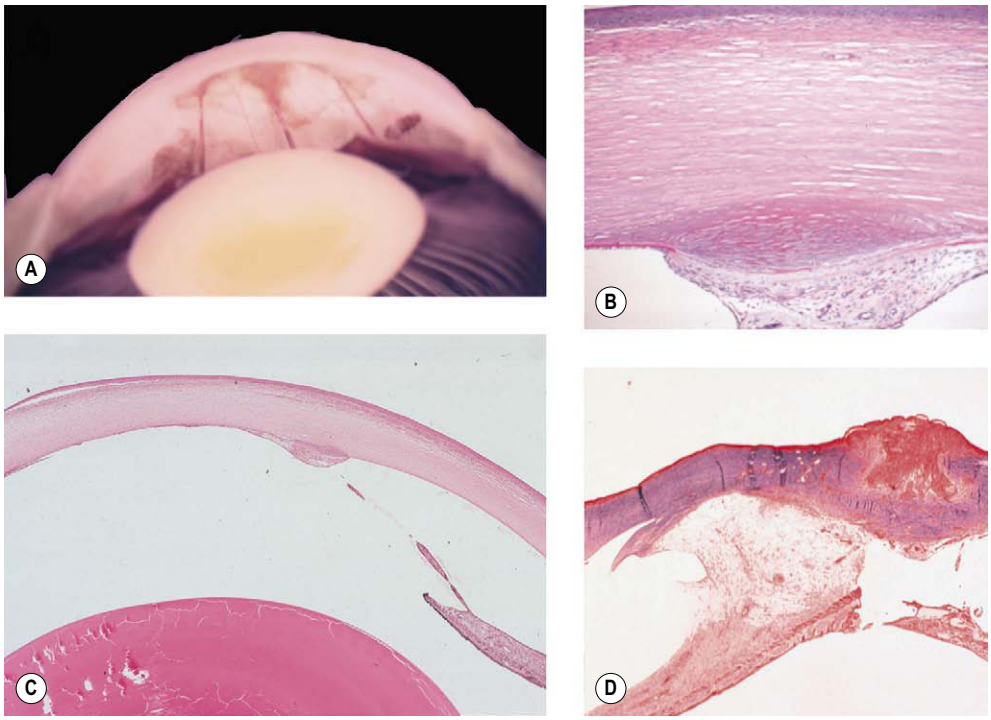


Figure 3.27 Peter's anomaly, pathology. (A) Gross photograph of a canine globe with Peter's anomaly. (B) Photomicrograph, of the dog in (A), showing the attachment point of a cord of uveal tissue to the posterior cornea. Descemet's membrane is discontinuous and uveal stroma blends into the corneal lamellar stroma. (C) Low magnification photomicrograph, of the dog in (A), showing delicate uveal cords spanning the anterior chamber. (D) Low magnification photomicrograph of another dog globe showing a broader sheet of uveal tissue stretched between the iris and posterior cornea. There is also deep invasion of the corneal epithelium into the lamellar stroma (trichrome stain). (Reproduced with permission from Swanson H L, Dubielzig R R, Bentley E et al 2001 A case of Peters' anomaly in a Springer spaniel. J Comp Pathol 125:326–30.)

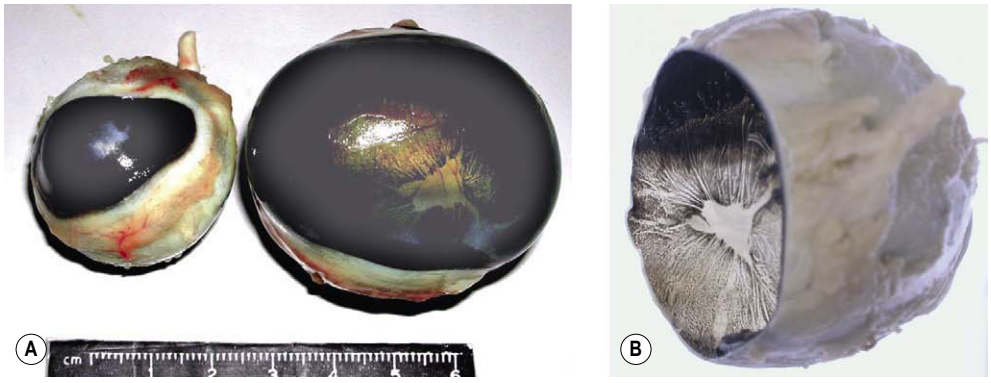


Figure 3.28 Anterior segment dysgenesis in a horse. (A) Gross photograph of both globes from a horse. While there is obvious asymmetry, both globes have anterior segment dysgenesis with a failure in the formation of the anterior chamber. (B) In the sectioned enlarged globe from (A), pigmented iris tissue is plastered against the posterior aspect of the cornea.

- In the COPLOW collection these diagnoses are made infrequently, as follows:
  - Canine early life trauma causing collapse of the anterior chamber: 23 cases
  - Canine anterior segment dysgenesis: 26 cases
  - Feline early life trauma causing collapse of the anterior chamber: 19 cases
  - Feline anterior segment dysgenesis: 16 cases
  - Equine anterior segment dysgenesis: 9 cases.

Iris coloboma (Fig. 3.29)

Congenital segmental defect in the formation of the iris, leading to an abnormal pupil shape or a focal absence of iris tissue.

Scleral coloboma (Fig. 3.30)

Congenital segmental scleral defect leading to outward bulging (ectasia) of the sclera. May be associated with strabismus due to abnormal extraocular muscle insertion.

Congenital corneal edema in association with multifocal defects in Descemet's membrane and endothelium (Fig. 3.31)

Rare cases of young animals with corneal edema and increased corneal thickness, otherwise unexplained, should be evaluated carefully for segmental defects of Descemet's membrane and endothelial cells embedded in the posterior stroma.

Comparative Comments

The spectrum of congenital abnormalities seen in different breeds in veterinary medicine is similar to that encountered in humans, however, there is no clearly discernable ethnic or racial predominance in humans.

On the other hand, the link between specific developmental disorders and the human genome is, in general, much better worked out.

For example, trisomy 13 (Patau's syndrome) is seen in one out of 14000 live births.

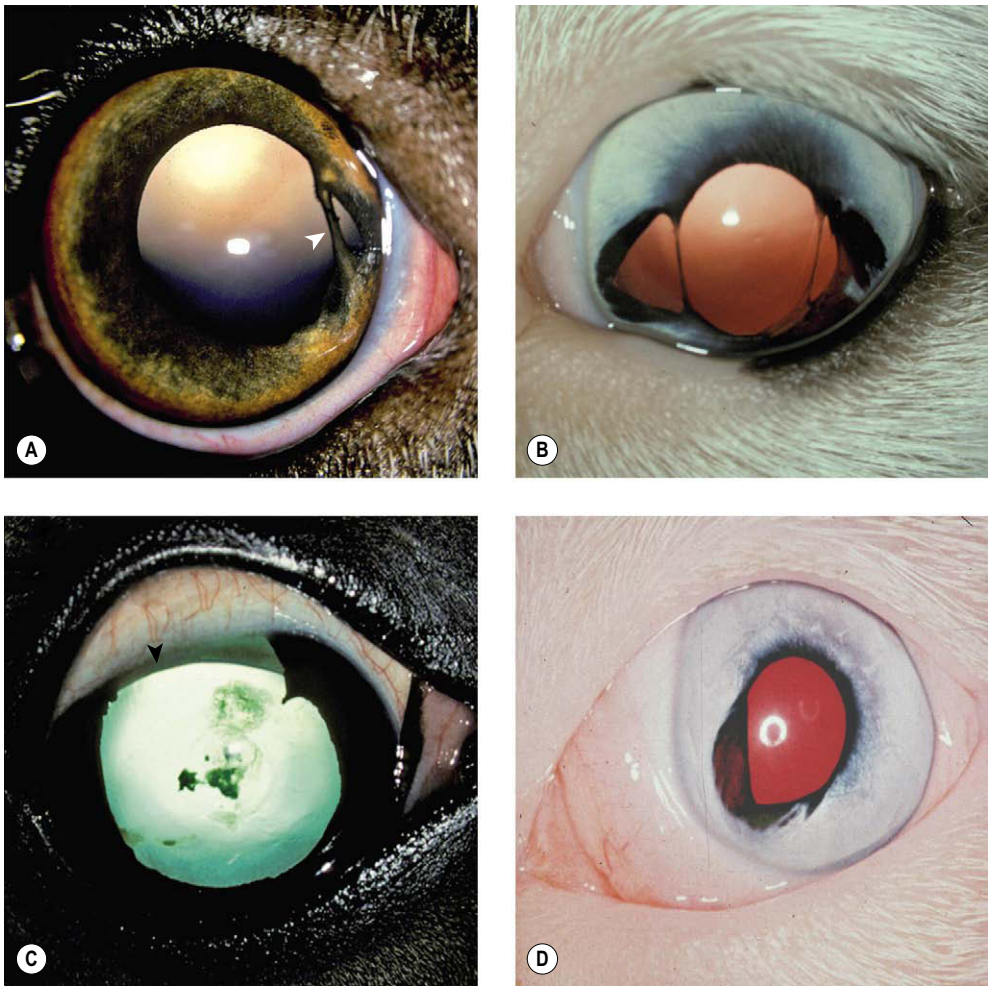


Figure 3.29 Iris coloboma. (A) Australian Shepherd, 1.5 years old: there is an iris coloboma at the arrow. (B) Australian Shepherd, 9.5 years old: two iris colobomas, at 3 o'clock and 9 o'clock, are visible. (C) Thoroughbred, colt: a superior coloboma resulted in visualization of the lens equator superiorly (arrow). (D) DSH, 1 year old: visualization of the posterior pigmented epithelium of the iris is possible due to a coloboma of the iris stroma.

SPORADIC CONGENITAL ABNORMALITIES OF UNDETERMINED ORIGIN

Microphthalmia syndromes

- Microphthalmos may arise early in development due to abnormal development of the optic vesicle, or later in development through failure to establish intraocular pressure which normally contributes to growth and expansion of the globe
- Microphthalmia in horses (Fig. 3.32):
  - There are six cases of congenital microphthalmia in horses in the COPLOW collection
  - This syndrome is seen sporadically in foals that are otherwise fully developed and without other, systemic abnormalities
  - The Thoroughbred is over-represented, but the condition has been observed in many breeds
  - There is no known or suspected cause, and this condition is not believed to be inherited
  - Affected animals are generally affected bilaterally but often not symmetrically
  - Ranges in severity from a small but otherwise normal eye, 'nanophthalmos', to extreme microphthalmos with multiple ocular anomalies
  - Microscopic findings may include:
    - Microphthalmos
    - Often see epidermal/hair follicular differentiation at the corneal limbus (dermoid)
    - Aphakia or profound microphakia
    - Failure to develop any normal anterior chamber
      - No Descemet's membrane
      - No normal corneal endothelium (ciliary and iridal epithelium is often present but disorganized or cystic)
    - Heterotopic development of fully differentiated tissue not appropriate to the globe in the anterior segment
      - Stratified squamous epithelium (can be cystic)
      - Glandular tissue
      - Cartilage.

Microphthalmia in white-tailed deer (Fig. 3.33)

- This condition shares many features of the condition in horses
- Affected fawns are well developed, with no identifiable congenital abnormalities in other systems
- There is no known cause, and there is no reason to believe that this condition is heritable. Environmental teratotoxicosis is suspected

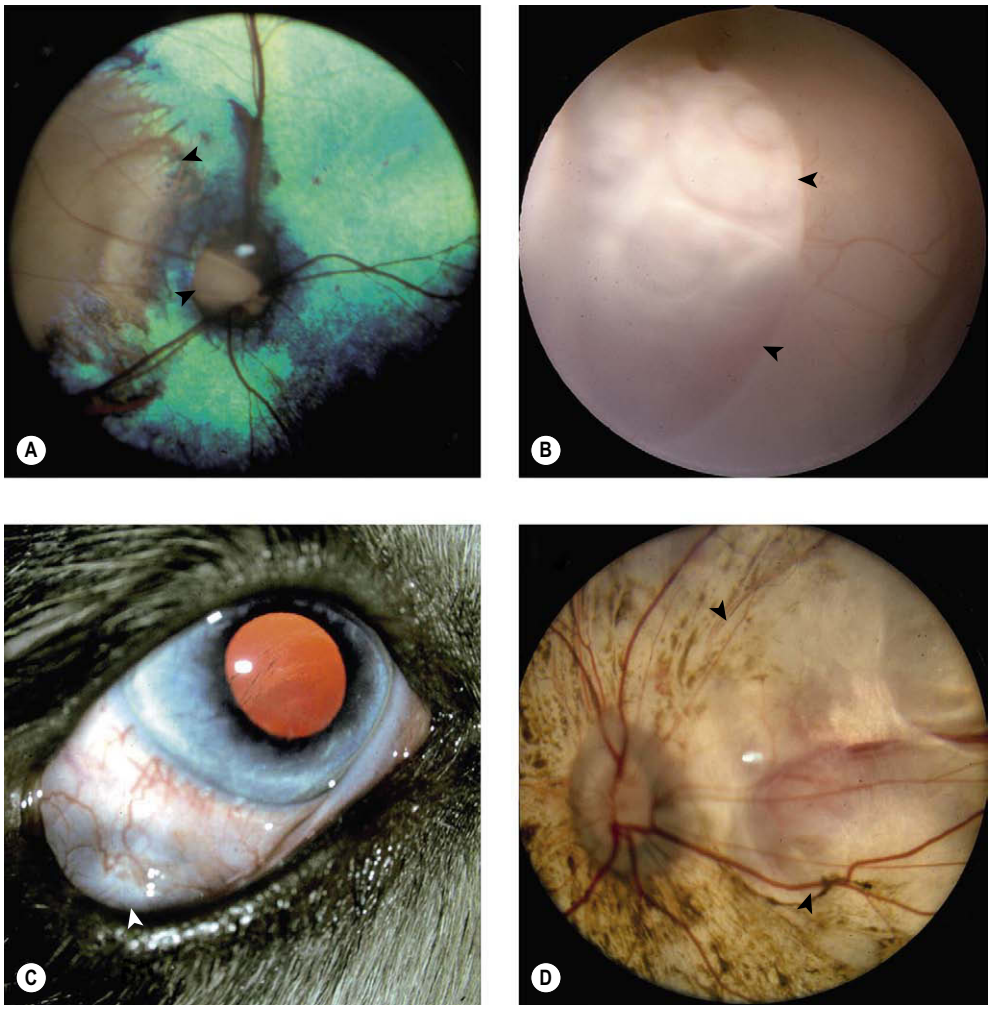


Figure 3.30 Scleral ectasia and coloboma. (A) DSH, 6 months old: a large temporal and a smaller peripapillary area are present at the arrows. An upper lid agenesis was also present. (B) Australian Shepherd, 2 years old: the arrows indicate a large area of scleral ectasia in the inferior nasal fundus. (C) Australian Shepherd, 2 months old: an area of scleral ectasia is present at the arrow. (D) American Eskimo dog, 6 years old: in the subabinotic, atapetal right fundus, a large staphyloma is present between the arrows. The condition was bilateral.

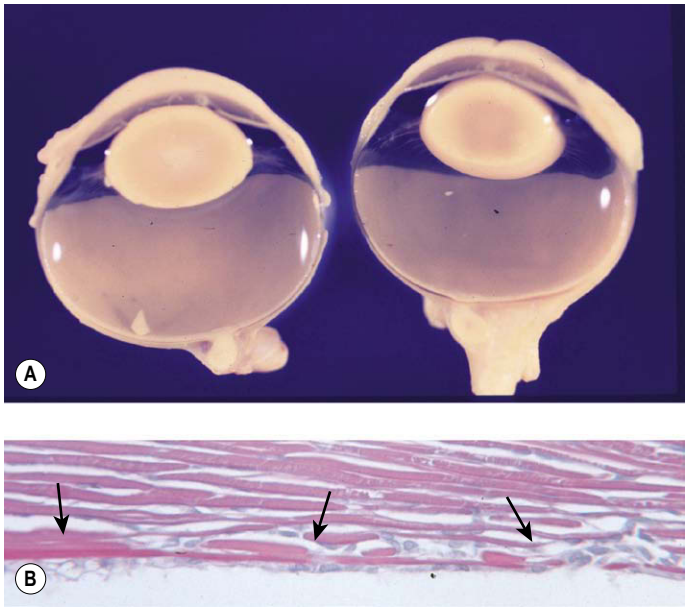
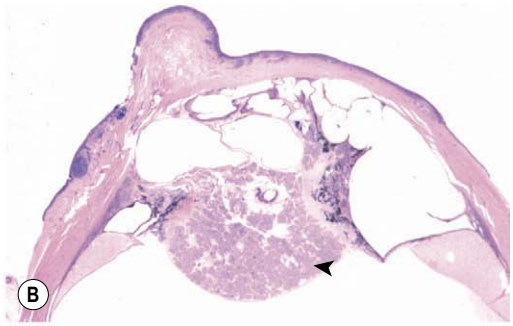


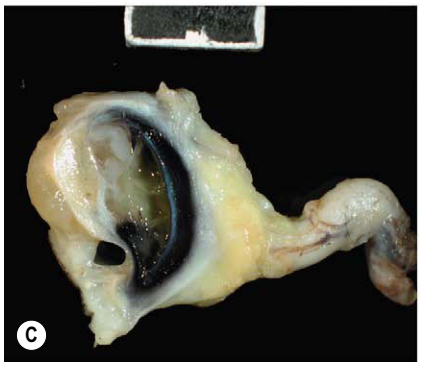
Figure 3.31 Canine congenital corneal edema. (A) Gross photograph of both globes from a dog with corneal edema and extreme thickening. (B) Photomicrograph showing interrupted Descemet's membrane (arrows) and dysplastic endothelium in a dog with congenital corneal edema.

- In Wisconsin, the condition is seen more commonly in areas where the land is used for intensive agriculture, with application of chemicals and intense irrigation. This may indicate a possible environmental cause

- Affected animals are always affected bilaterally but not always symmetrically
- Morphologic abnormalities include:
  - Microphthalmos
  - Opaque and pigmented cornea
  - Aphakia, except focal differentiation of dysplastic lens cells
  - Failure to develop any normal anterior chamber
    - The deep corneal stroma resembles sclera in appearance
    - No Descemet's membrane
    - No normal corneal endothelium
    - Normal but disorganized iridal or ciliary epithelium may be present
  - Heterotopic development of fully differentiated tissue not appropriate to the globe within the anterior segment
    - Stratified squamous epithelium
    - Glandular tissue
    - Of 30 specimens examined from Wisconsin, no cartilage tissue was found. However, cartilage has been reported in eyes of fawns from other states
  - Severely disorganized neuroretinal tissue often extends across the posterior aspect of the abnormal tissues of the anterior







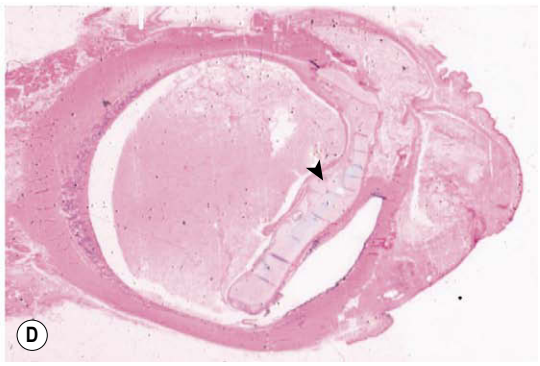
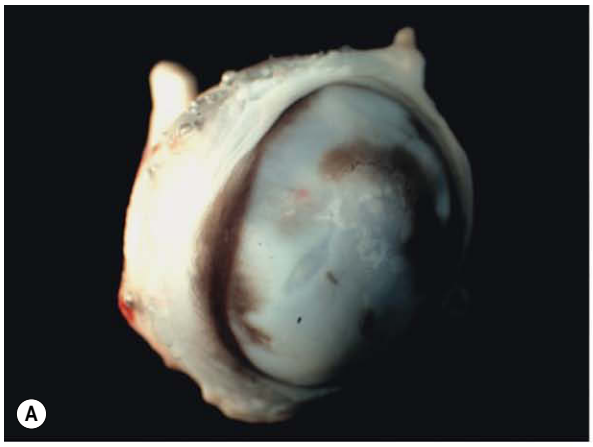
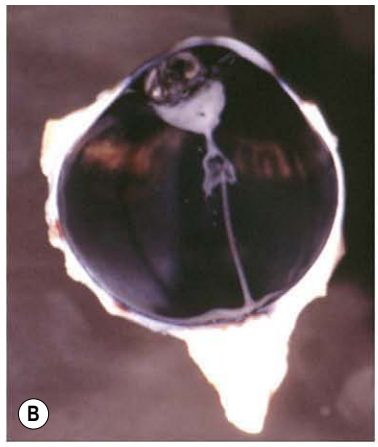
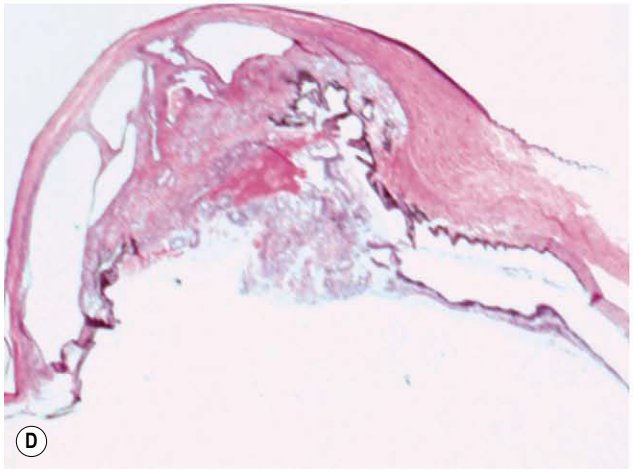


Figure 3.32 Congenital equine microphthalmos. (A) Gross photograph showing both globes from a horse with congenital equine microphthalmos. (B) Subgross photomicrograph of an equine globe with congenital microphthalmos. There is no formed anterior chamber, no lens tissue, and a large glandular structure occurs in the center of the image (arrow). (C) Gross photograph of a severely microphthalmic and aphakic equine globe. (D) Subgross photomicrograph of a microphthalmic and aphakic equine globe showing cartilage tissue within the globe (arrow).









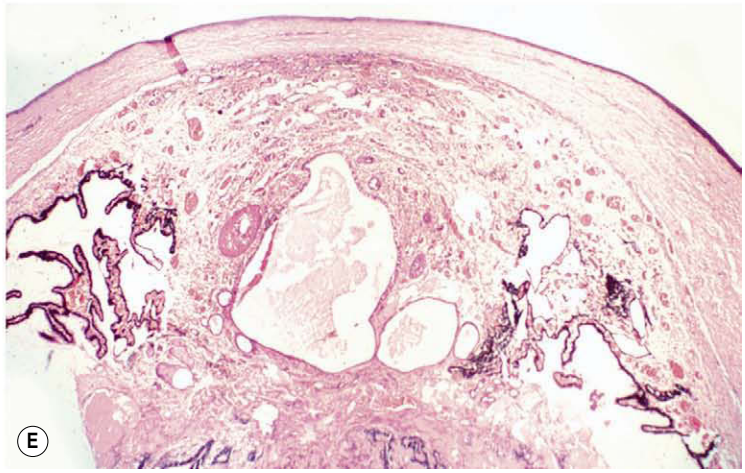


Figure 3.33 Congenital microphthalmos in white-tailed deer. (A) This microphthalmic white-tailed deer globe has a partially pigmented cornea. (B) A sectioned white-tailed deer globe showing no lens, no anterior chamber and a persistent hyaloid vascular remnant. (C) Subgross photomicrograph of the globe in (B) showing absence of lens and abnormal tissues in the collapsed anterior uvea. (D,E) Low magnification photomicrographs of white-tailed deer globes show no lens. Sheets of disorganized tissue in the anterior segment include glandular tissue, stratified squamous epithelium and gliotic neuroretinal tissue.

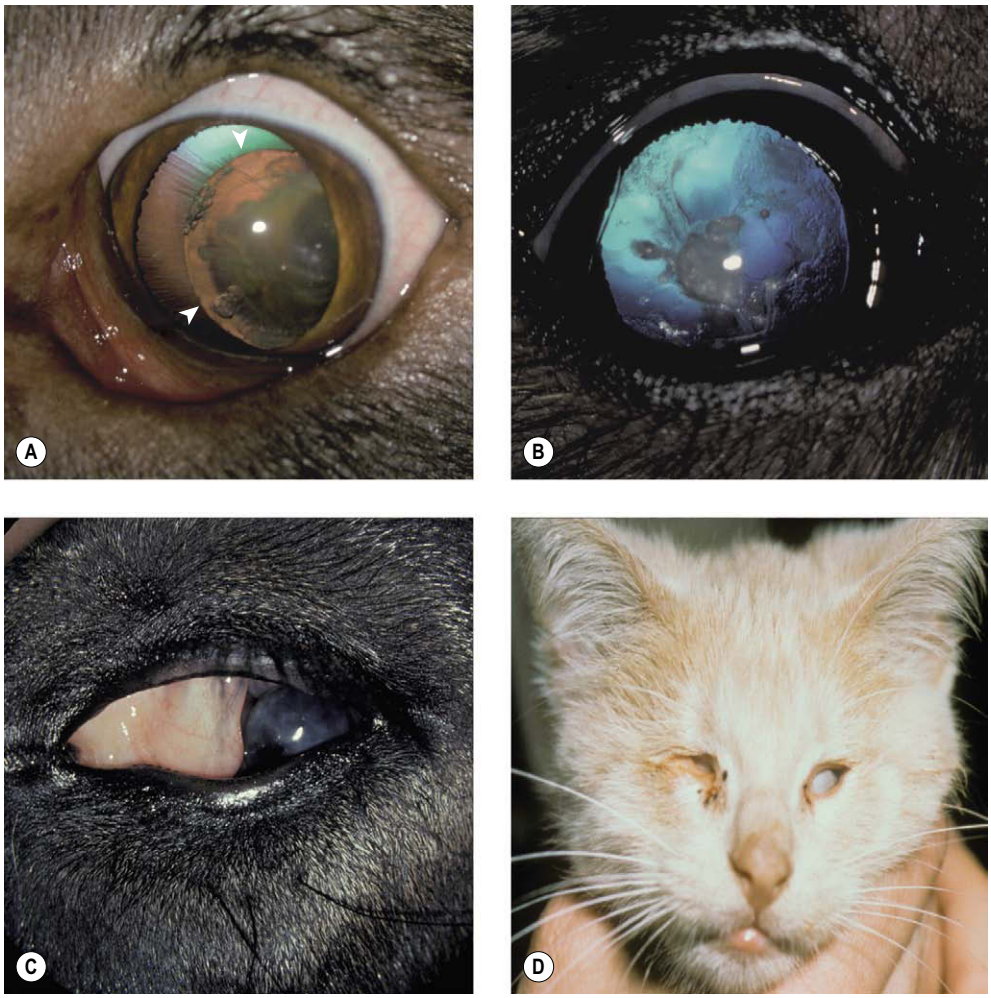


Figure 3.34 Microphthalmos in several species, clinical. (A) Labrador Retriever, 6 months old: in this bilateral case, the nictitans is slightly prolapsed and the small cataractous lens is sub-luxated (arrows) with visible zonular fibers. (B) Miniature Schnauzer, 4 months old: a diffuse nuclear and cortical cataract is associated with the unilateral microphthalmia. (C) Thoroughbred, foal: the nictitans is prolapsed in this case of severe microphthalmia. (D) DSH, 3.5 years old: in addition to the reduced palpebral fissure and small globes, both pupils had dyscoria and immature cataracts were present.

segment. Within this disorganized neural tissue, there is often dysplastic lenticular differentiation.

Sporadic microphthalmic syndromes (Fig. 3.34)

Microphthalmos, with variable associated ocular anomalies, such as anterior segment dysgenesis, cataract, persistent pupillary membranes, PHPV/PHTVL, coloboma or retinal dysplasia, may be seen as a sporadic finding in any species.

Feline neovascular vitreoretinopathy (Fig. 3.35)

There are 10 cases of feline neovascular vitreoretinopathy in the COPLOW collection.

- This condition is generally not recognized until glaucoma develops at 6 months to 3 years of age, however the peripheral retina remains avascular which suggests that the condition is, indeed, congenital
- The hallmark lesions:
  - Complete retinal detachment
  - Unilateral in all affected animals to date
  - Neovascular membranes within the vitreous body
  - An avascular peripheral retina
  - Pre-iridal fibrovascular membrane and peripheral anterior synechiae
- This syndrome shares many morphologic features with retinopathy of prematurity (ROP) in humans, which is also discussed in Chapter 11
  - The ROP is a major concern in premature infants subject to positive pressure ventilation with supplemental oxygen in the management of respiratory distress. In ROP the normal post-natal development of retinal blood vessels is interrupted because vasoconstriction occurs when hyper-oxygenated blood circulates in the retinal vasculature
    - This leads to local hypoxemia and subsequent neovascular tufts which extend into the vitreous rather than developing along the inner retina
    - Traction from the resulting neovascular membranes may lead to retinal detachment and blindness
    - ROP is easily induced in newborn kittens by exposure to increased oxygen tension and then withdrawal
    - In the spontaneous feline disease, there has been no known history of perinatal difficulties.

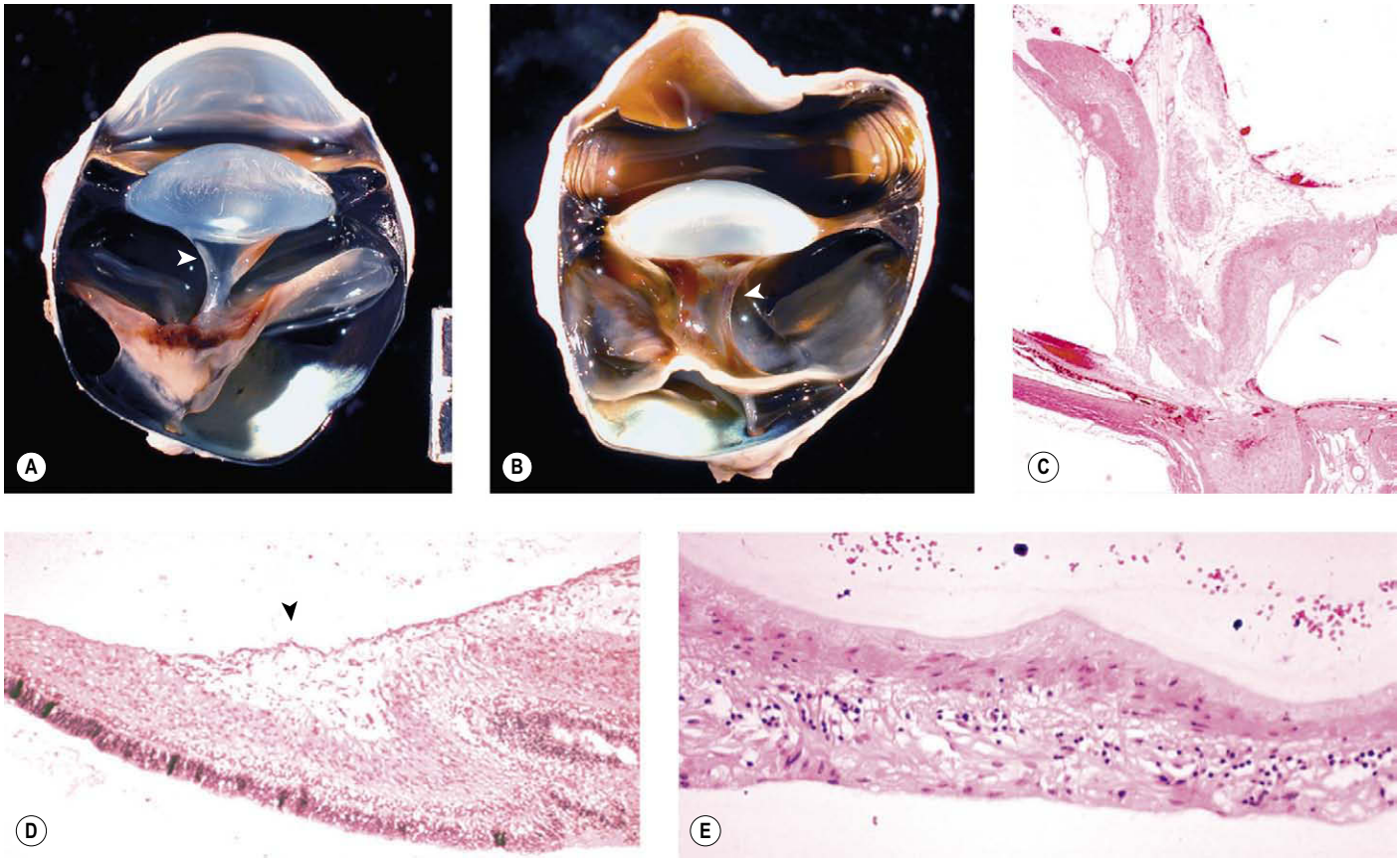


Figure 3.35 Feline neovascular vitreoretinopathy. (A,B) Photomicrographs of feline neovascular vitreoretinopathy in two cats. There is a vascularized intravitreal membrane internal to the detached retina (arrows). (C) Low magnification photomicrograph showing the detached retina and a vascularized membrane in the central and posterior retina. (D) Photomicrograph showing gliotic retina with a vascularized vitreal membrane on the inner surface (arrow). (E) Photomicrograph showing a gliotic peripheral retina with no blood vessels.

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Chapter 4

Surgical trauma and iatrogenic lesions

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COMPLICATIONS OF INTRAOCULAR SURGERY

Of submissions in the COPLOW archive, 1.3% are related to complications of surgery.

General categories of surgical complications

Intraoperative complications leading to submission of specimens to the pathology laboratory (Fig. 4.1):

- Expulsive choroidal hemorrhage (Fig. 4.1)
  - Rapid hemorrhage in the suprachoroidal space in an open, decompressed globe causes expulsive anterior displacement of ocular tissues, and is a devastating complication
    - This is associated with the sudden onset of ocular hypotony
    - In the COPLOW collection, this is often seen in association with acute non-surgical trauma. This could reflect a failure to submit surgical cases, or may indicate that this is a rare complication of intraocular surgery in animals
    - Fortunately, when this is seen in the COPLOW collection as a surgical complication, it is usually in eyes where the sclera was inadvertently cut during an enucleation procedure
- Evisceration procedures aborted due to unanticipated findings or procedural complications
  - The COPLOW collection contains 29 cases where evisceration surgery has been aborted and enucleation of the partially collapsed globe performed
    - All but three of these submissions were from evisceration procedures aborted by the surgeon because evidence of neoplastic or active inflammatory processes was encountered.

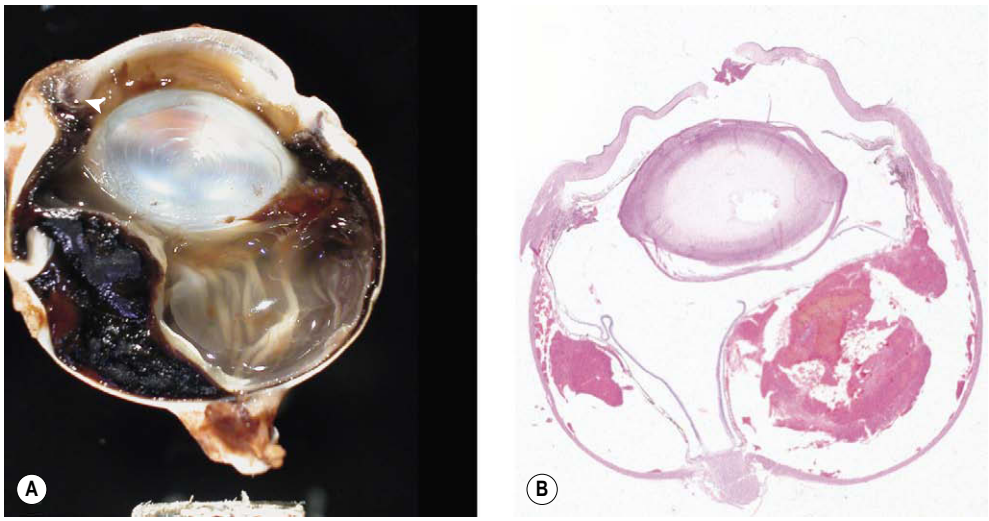


Figure 4.1 Acute trauma, expulsive choroidal hemorrhage. (A) Gross photograph of a canine globe with a penetrating traumatic injury (arrow) and expulsive hemorrhage in the choroid. (B) Subgross photomicrograph of a canine eye showing expulsive choroidal hemorrhage, which occurs when the pressure in the globe rapidly decreases.

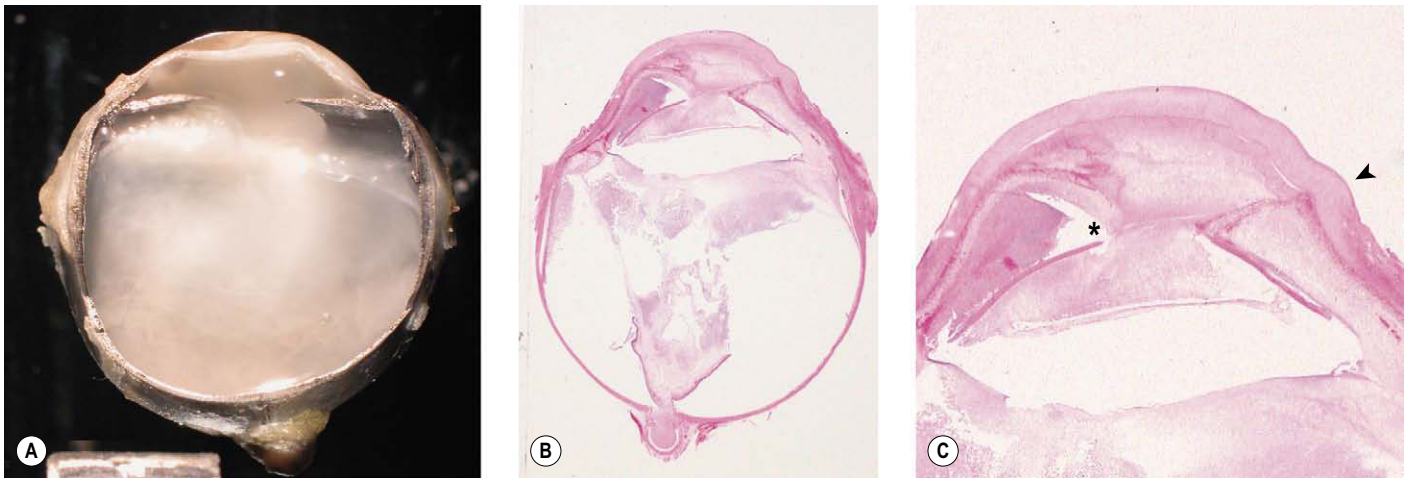


Figure 4.2 Postoperative inflammation. (A) Gross photograph of severe endophthalmitis/vitreitis, which occurred after cataract surgery in a dog. (B,C) Subgross and low magnification photomicrographs of the same canine globe show suppurative endophthalmitis and posterior synechia (*). The arrow in (C) points to the surgical incision.

Inflammation associated with known or presumed infection or toxic contamination during surgery (Figs 4.2–4.4)

- 'Outbreaks' of endophthalmitis in multiple consecutive, or nearly consecutive, cases from the same practice
  - COPLOW has examined a series of cases from three such outbreaks
    - Contamination or manufacturing defects in viscoelastic (one series) and prosthetic intraocular lenses (two series) were implicated as sources of intraocular contamination
    - Endophthalmitis was recognized clinically within a few days of the surgical procedure and progressed rapidly
    - Suppurative, neutrophilic endophthalmitis centered on the anterior segment
    - Delayed healing of the surgical incision and suture track inflammation were seen in several of the globes. In these cases, incisional abnormalities were assumed to be secondary to endophthalmitis. However, as definitive cause-and-effect relationship could not be established, incisional complications may also have directly contributed to the development of endophthalmitis
    - Only a single case from one of the series had histologically demonstrable bacteria, identified in the vitreous near the posterior lens capsule
- Sporadic endophthalmitis following intraocular surgery (Fig. 4.2)
  - There are 40 cases in the COPLOW database
  - Affected globes were typically enucleated between 3 days and 3 months postoperatively
    - Those cases, in which enucleation occurred within 7 days of intraocular surgery, had intraocular sepsis, based on direct observation of bacterial organisms
    - The cases in which enucleation took place more than seven days postoperatively seldom had demonstrable sepsis
  - These cases often had evidence of severe corneal pathology, that included (Figs 4.3, 4.4):
    - Dehiscence of the surgical incision
    - Suture tract suppuration

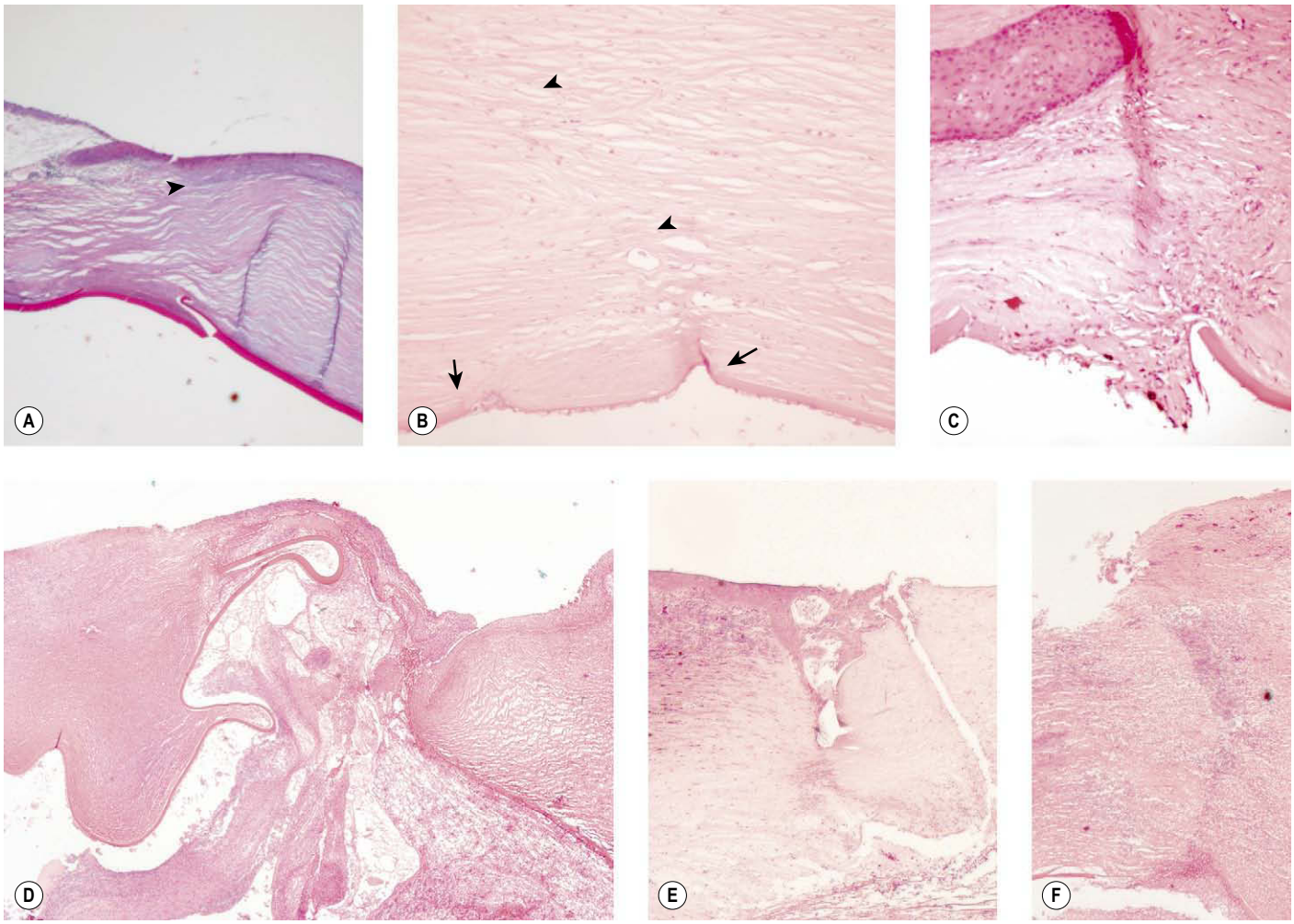


Figure 4.3 Complications of the corneal surgical incision. (A,B) Photomicrographs showing the keratotomy site in canine cataract surgery without complications from the surgical incision (arrowheads). The small arrows point to the ends of a break in Descemet's membrane. (C) Photomicrograph of the inner aspect of a canine cataract surgery corneal incision showing mild fibroblast proliferation, vascularization, and corneal epithelial down-growth. (D–F) Three photomicrographs of cataract surgery corneal wounds. Varying degrees of suppurative inflammation are severe enough to cause intraocular complications or wound dehiscence.

  - Collagenolytic keratitis
  - Stromal abscessation
  - Perforation away from the surgical wound.

Long-term postoperative complications (manifesting long after the surgery) (Figs 4.5–4.9)

- Implantation of corneal or conjunctival epithelium, within the corneal stroma leading to the formation of inclusion cysts (Fig. 4.5)
  - Epithelial inclusion cysts present as focal, opaque nodules in the cornea at the site of surgery or other trauma (see also Ch. 8)
  - Histologically, inclusion cysts are bland, localized nodules that have a lining of fully-differentiated epithelium and are often filled with keratin or mucin
- Corneal edema associated with endothelial damage
  - Corneal edema associated with compromised endothelial function causes pronounced stromal thickening, a blue/white corneal opacity, and an increased susceptibility to infection as well as an increased risk of collagenolysis
  - Intraocular surgery is a major hazard to the corneal endothelium, which has limited or no regenerative potential in adults
  - Direct mechanical contact can be harmful to the endothelium
  - Separation of the endothelium from the stroma during surgery can also be harmful
  - Exposure to irrigating solutions, viscoelastic materials (used to protect the endothelium and help maintain the anterior chamber intraoperatively), or other pharmacologic preparations can be harmful to the endothelium, particularly if contaminated with endotoxin, or if contact with the endothelium is prolonged. Permanent damage to the endothelium is unlikely when irrigation solutions such as saline or balanced salt solution are used in limited volumes (100 mL or less) over limited periods of time
  - Morphologic changes seen in the corneal endothelium after intraocular surgery include (Fig. 4.6):
    - Attenuation
    - Spindle cell metaplasia and retrocorneal membrane formation

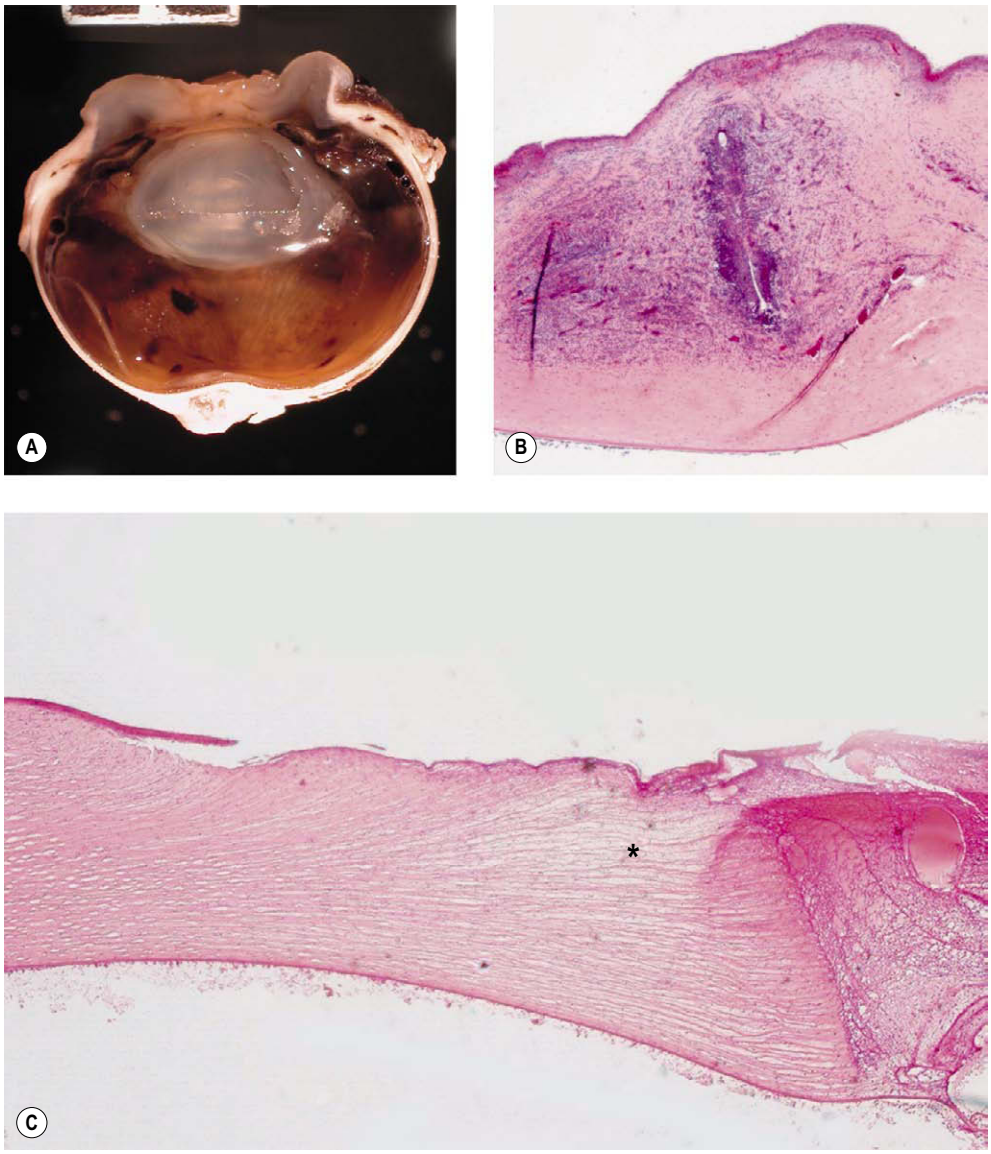


Figure 4.4 Collagenolysis. (A) Gross photograph of a canine globe with collagenolysis of the axial corneal stroma. (B) Photomicrograph of a canine globe with a mid-stromal abscess. (C) Acute collagenolysis (*) in an affected canine cornea.

  - Duplication of Descemet's membrane
    - The mechanism of this duplication is not clear, but it is commonly observed after surgery or blunt trauma. Endothelial separation and reattachment may induce duplication of Descemet's membrane
    - This morphologic feature may also be seen following non-surgical trauma (discussed in Ch. 5).
  - Multiple breaks in Descemet's membrane (striate keratopathy)
    - Manipulation and bending of the cornea during surgery can cause Descemet's membrane to rupture
- Intravitreal traction bands and retinal detachment
  - Disruption of the vitreous and low-grade inflammation in the globe lead to fibrous bands (traction bands) across the anterior vitreous and subsequent retinal detachment (Fig. 4.7)
  - Vitreal traction bands are more likely to occur if there is inflammation or hemorrhage in the postoperative period
- Glaucoma (Fig. 4.8)
  - Neovascular glaucoma
    - Retinal detachment is associated with the release of the growth factors, vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF). Soluble VEGF, in particular, stimulates pre-iridal fibrovascular membrane formation. This, in turn can cause peripheral anterior synechiae and the development of neovascular glaucoma
  - Glaucoma secondary to posterior synechiae (iris bombé)
  - Glaucoma secondary to anterior synechiae
  - 'Malignant glaucoma' may occur in the immediate postoperative period, or as a longer-term complication. This may result from disruption and posterior misdirection of aqueous humor flow by anteriorly prolapsed vitreous, and/or inflammatory membranes extending across the anterior vitreous face, ciliary body (cyclitic membranes) or pupil, in eyes following lens or cataract extraction

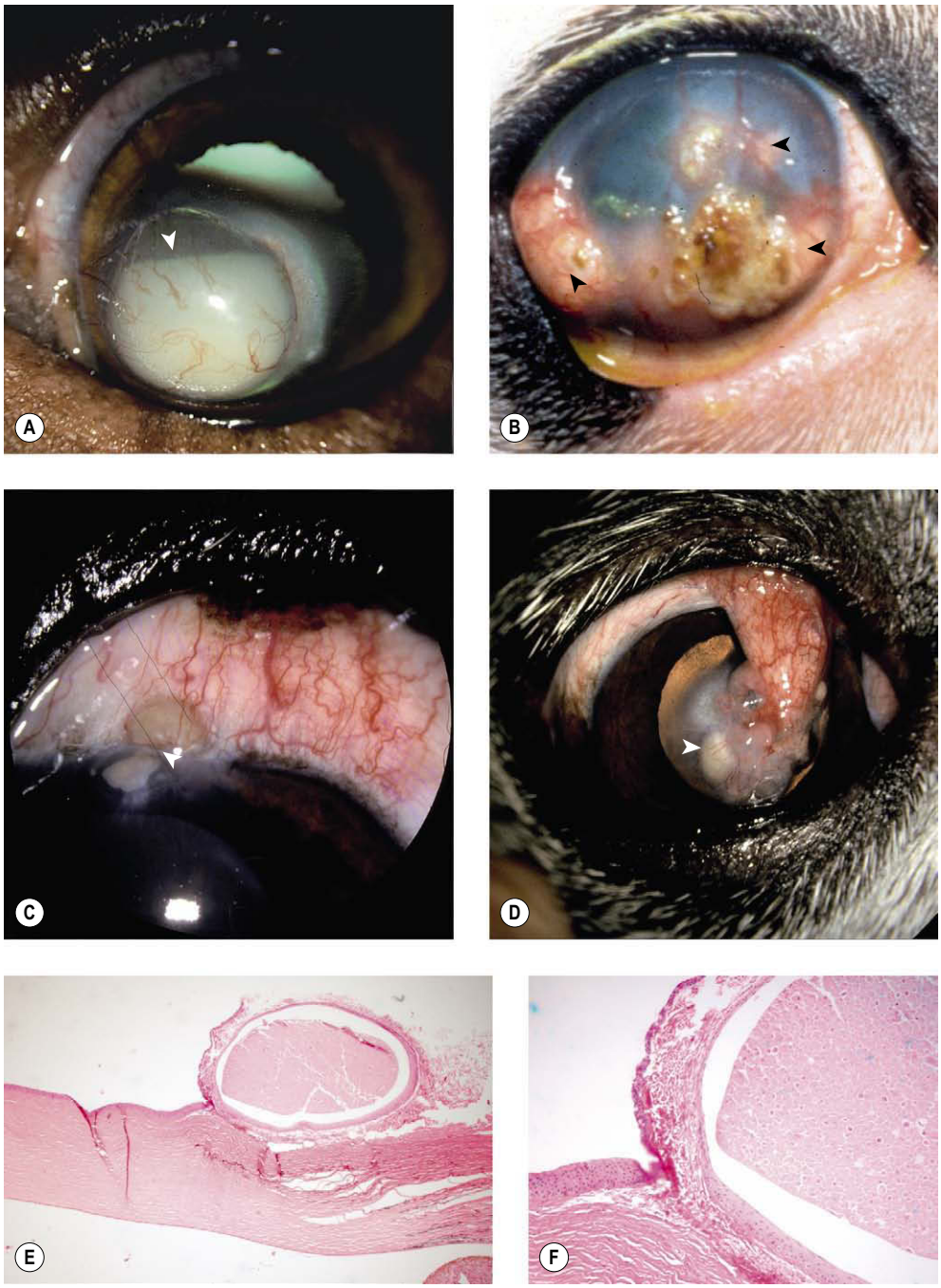


Figure 4.5 Epithelial inclusion cysts. (A) German Shorthaired Pointer, 6 years old: following trauma, this large cyst developed. Epithelial cells can be seen settling in the cyst (arrow). (B) Boston Terrier, 3 years old: multiple inclusion cysts are present (arrows) following a grid keratotomy. (C) German Shepherd Dog, 12 years old: limbal inclusion cysts are present (arrow) following a limbal incision for lens extraction. (D) Boston Terrier, 9 years old: the cyst (arrow) formed following the placement of a conjunctival flap. (E,F) Photomicrographs of an epithelial inclusion cyst embedded in the substantia propria of canine limbal conjunctiva.

- Epithelial down-growth and epithelial lining of the globe (Fig. 4.9)
  - The surface epithelium can gain entry to the globe through the surgical incision or through suture tracts. In many instances, its presence signals poor incision closure technique
  - Once stratified squamous epithelium or conjunctival epithelium is introduced into the globe, it can slowly cover the internal surfaces of the ocular tissues, interfering with their function, stimulating inflammation in response to released keratin, or obstructing aqueous flow
  - Entrapped fragments of epithelium can become cystic within the corneal or scleral stroma, forming epithelial inclusion cysts.

Comparative Comments

A greater proportion of human eyes submitted for pathology have had intraocular surgery as compared with the COPLOW eyes. Few of these human eyes, however, are submitted because of direct complications of intraocular surgery. Rather, in human eyes, multiple operations are commonly done to avoid blindness following non-surgical trauma or to prevent further vision loss in conditions such as glaucoma, retinal detachment, or retinal vascular disease. Expulsive choroidal hemorrhages, endophthalmitis, corneal decompensation, retinal detachment, glaucoma, and epithelial in-growth are all feared complications of intraocular surgery that are encountered in human specimens as well as in animals.

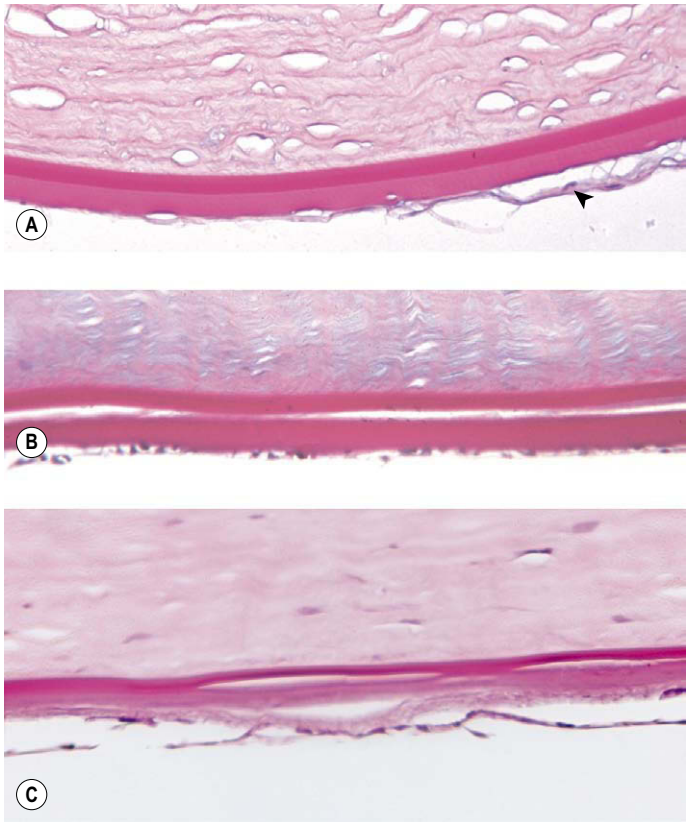


Figure 4.6 Corneal endothelial and Descemet's membrane changes. (A) Photomicrograph showing a Descemet's membrane with distinct anterior and posterior components and a retrocorneal membrane (arrow) consisting of spindle cells, which replace the native endothelium. (B) Photomicrograph showing complete duplication of the Descemet's membrane. The endothelium is still recognizable but attenuated. (C) Descemet's membrane has a variable thickness and blends with a retrocorneal membrane anterior to the attenuated endothelium (PAS stain).

THE FULL-THICKNESS CORNEAL INCISION AND ITS VARIATIONS

Morphologic features of the uncomplicated corneal incision (Fig. 4.10)

- In the first few weeks after surgery, a granulomatous response to suture material within cornea may be seen. Suppurative response and epithelialization of suture tracts may be greater with absorbable (e.g. polyglactin 910) than with non-absorbable (e.g. monofilament nylon) suture materials
- With good apposition, there is minimal scar formation in the corneal stroma, and recognizing the incision site is difficult, unless the submitting clinician clearly identifies its location. Below are clues to identifying the healed, uncomplicated surgical wound:
  - Identify the break in Descemet's membrane
    - In a surgical incision or traumatic rupture of the cornea, there is often recoil of the membrane which causes it to have curved edges
  - Examine the corneal surface, looking for any evidence of disruption to the epithelial basal lamina, or of epithelial down-growth
  - Using low magnification, look for a full-thickness, lineal disruption in the regular, lamellar structure of the normal corneal stroma.

Iridal entrapment or prolapse (Fig. 4.11)

- Due to the hypotonic nature of the opened globe that leads to anterior displacement of iris tissue, or because the iris was inadvertently pulled into the incision during closure, it is not unusual to find iris tissue entrapped in the incision. Subsequently, these uveal remnants will become incarcerated in the incisional scar tissue
  - This entrapment causes delayed or imperfect wound healing, focal corneal opacity and anterior synechiae. The latter may contribute to postoperative glaucoma if extensive.

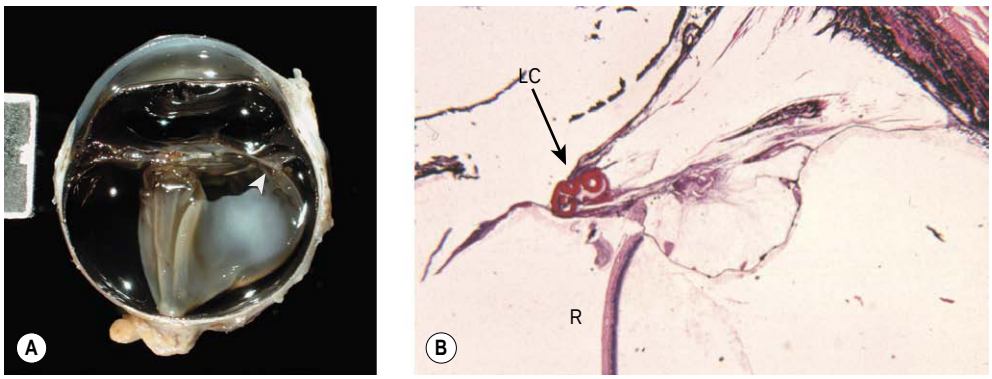


Figure 4.7 Retinal detachment. (A) Gross photograph of a canine globe showing retinal detachment associated with traction bands (arrow) between the lens capsular bag and the peripheral retina. (B) Low magnification photomicrograph showing the peripheral retina (R) pulled toward the lens capsular bag (LC and arrow) because of a contracting spindle cell membrane (PAS stain).

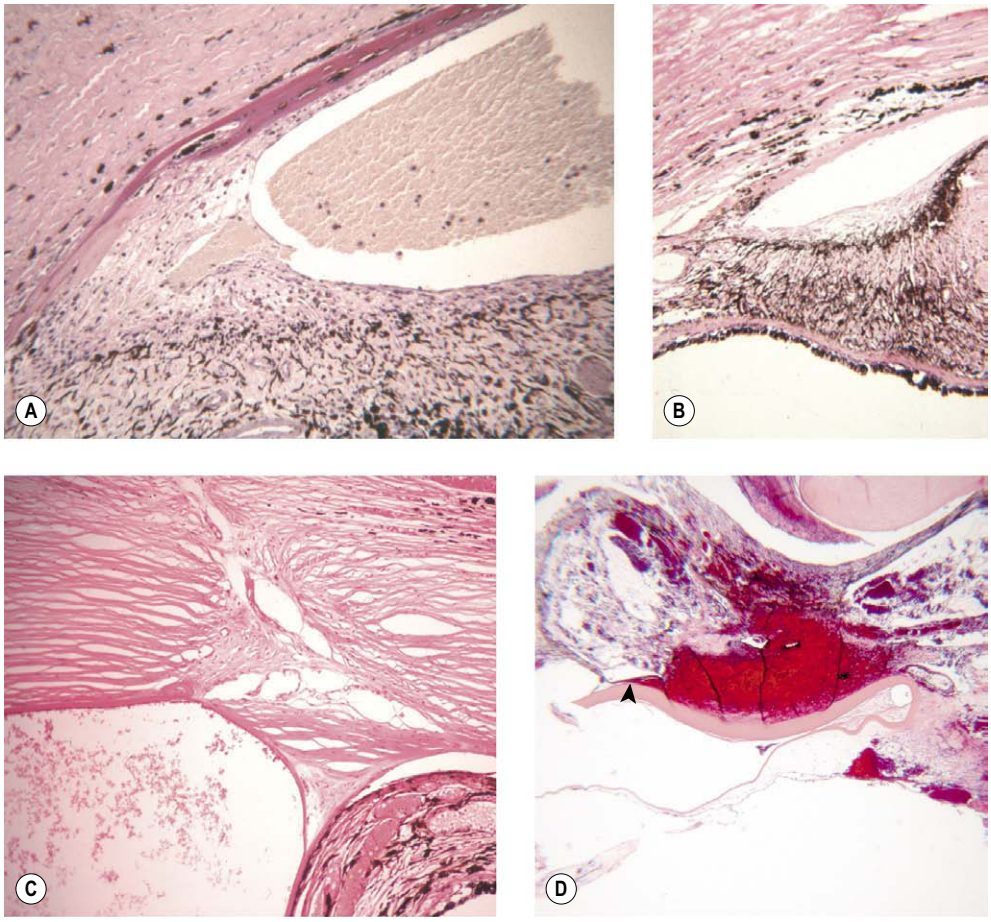


Figure 4.8 Glaucoma. (A,B) Photomicrographs of canine iris and iridocorneal angle show pre-iridal fibrovascular membrane and peripheral anterior synechia leading to neovascular glaucoma. (C) Photomicrograph of a dog eye showing anterior synechia at the surgical scar contributing to angle closure. (D) Low magnification photomicrograph of a dog eye showing hemorrhage and posterior synechia between the iris and the lens capsular bag (arrow) causing pupillary block.

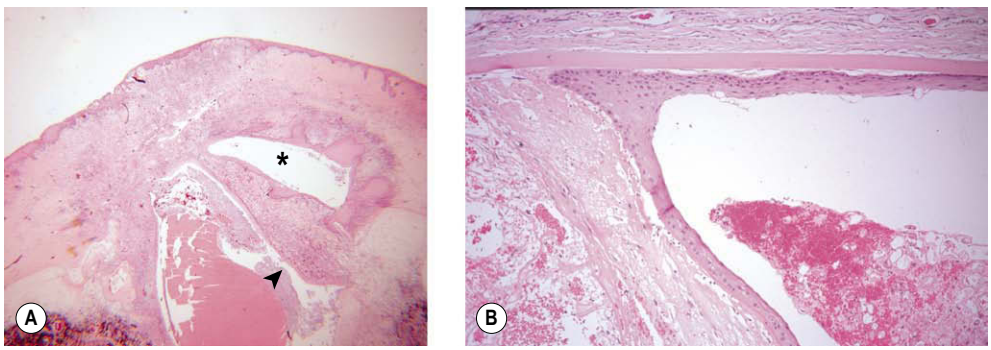


Figure 4.9 Epithelial down-growth. (A) Photomicrograph of a dog eye showing severe corneal inflammation at the surgical incision, with granulation tissue and epithelial down-growth that form a pocket within the deep stroma (*) and also within the anterior chamber (arrow). (B) Photomicrograph of a dog eye with fully-differentiated stratified squamous epithelium in the anterior chamber associated with pre-iridal fibrovascular membrane and broad anterior synechia.

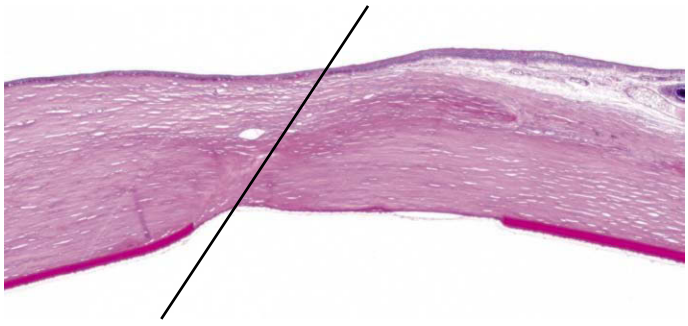


Figure 4.10 Uncomplicated corneal incision. Photomicrograph showing an uncomplicated corneal incision scar in a canine cornea indicated by the line.

Adverse reactions around sutures (Fig. 4.12)

- Epithelial down-growth
- Inflammation.

Wound dehiscence

- Dehiscence of the surgical incision is usually seen in conjunction with inflammation
- Consequences of dehiscence of the corneal incision
  - Delayed healing of the incision
  - Weakened surgical scar
  - Corneal opacity
  - Introduction of sepsis leading to endophthalmitis.

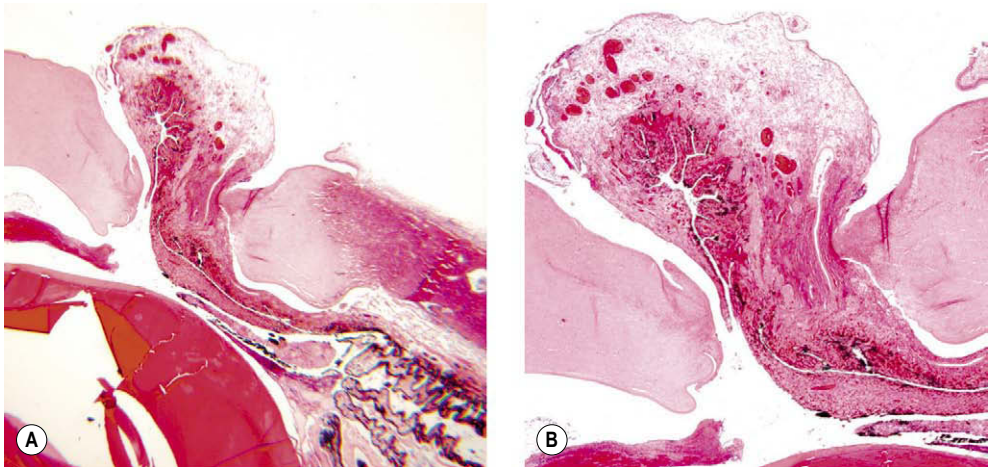


Figure 4.11 Corneal perforation and iris prolapse. (A,B) Photomicrographs of the same dog eye viewed at different magnifications show iris prolapse into the surgical incision causing acute surgical wound dehiscence.

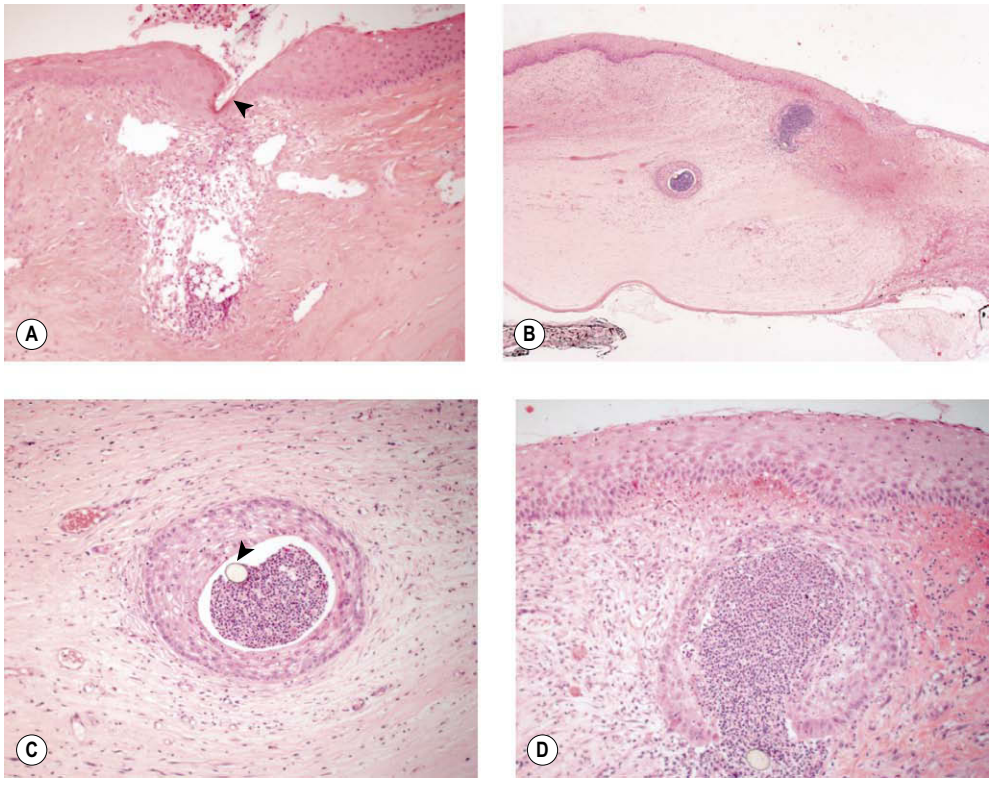


Figure 4.12 Epithelial down-growth and inflammation around sutures. (A) Photomicrograph showing suppurative inflammation in the corneal stroma where the suture (arrow) penetrates the cornea. (B) Low magnification photomicrograph showing epithelial down-growth and suppurative inflammation in a suture track. (C,D) Higher magnification photomicrographs show the same suture track as in (B). The arrow points to the monofilament suture in (C).

Aspiration or injection sites (Fig. 4.13)

- Injection or aspiration sites are often sampled as part of the protocol in studies involving intraocular injection or aspiration
- Although properly performed injections or aspirations have a low rate of complications, no procedure is entirely 'safe'. It is instructive to look at the local tissue reactions that occur at the site of such a common and, seemingly, innocuous procedure
- Lesions that may be seen at aspiration or injection sites include:
  - Disruption of scleral collagen
  - Phagocytosis of hypodermic needle lubricant, recognized as refractile, non-staining material
  - Glial and spindle cell proliferation within the vitreous
  - Vitreous prolapse into the site (this is more likely with aspiration techniques)
  - Epithelial down-growth.

Comparative Comments

Following the advent of microscopic surgery, iris incarceration or prolapse, suture problems, and wound dehiscence are extremely rare occurrences in human eyes submitted to the pathology laboratory.

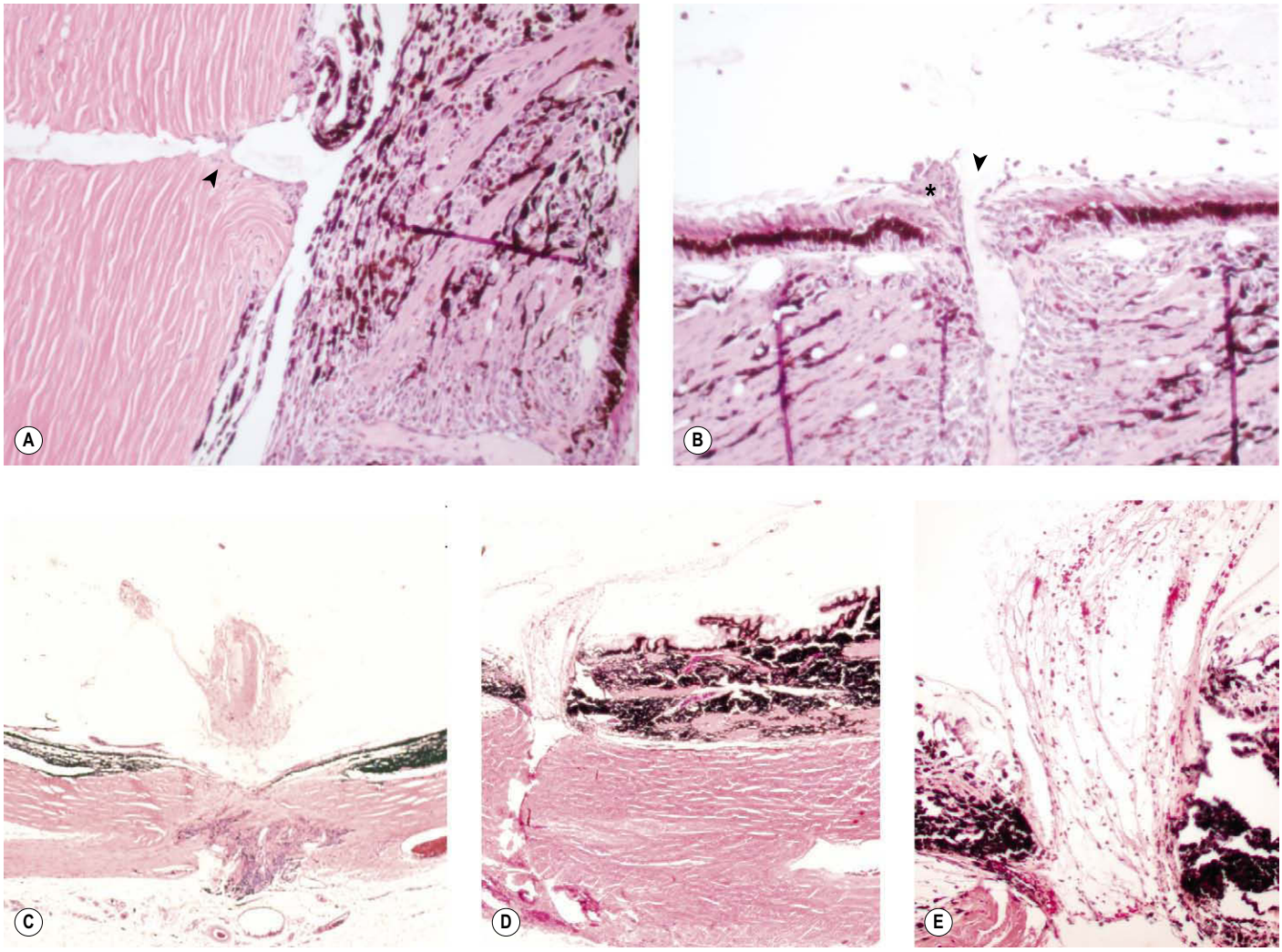


Figure 4.13 Injection and aspiration sites. (A) Photomicrograph showing the scleral aspect of a pars plana injection site in a primate eye. Small numbers of bland macrophage cells are seen within the cavitated area of the sclera (arrow). (B) Photomicrograph showing the ciliary body aspect of the same injection site as (A). There is a defect in the ciliary body epithelium (arrow) and an early reactive proliferation of spindle cells and glial cells (*). (C) Photomicrograph of a pars plana injection site in a canine globe showing an inward proliferation of spindle cells and/or glial cells. (D,E) Aspiration site in a canine globe. In this case, the aspiration was performed immediately before enucleation, but vitreous pulled into the aspiration defect might have complicated healing.

TISSUE EFFECTS OF ELECTROCAUTERY, CRYOSURGICAL AND LASER APPLICATIONS

The effects of electrocautery (Fig. 4.14)

- Used for surgical cutting and hemostasis
- Electrocautery creates a tissue artifact that the pathologist needs to be aware of when interpreting histopathological findings
  - Electrocautery affects the tissue immediately in contact with the device, regardless of the tissue type
  - These effects are seen at surgical margins where electrical energy was used for cutting or hemostasis
  - Electrocautery imparts a coagulation effect on connective tissues, seemingly fusing the collagen and other protein structures
  - The effect on epithelia is to cause cells to elongate into a distorted, spindle cell profile.

The effects of cryotherapy

- Used for focal ablation of ciliary body tissue in glaucoma; for retinopexy in the treatment or prevention of retinal detachment; treatment of mass lesions, including corneal, limbal and adnexal neoplasms, and in the management of distichiasis. Cryogens used in ophthalmic practice include liquid nitrogen, nitrous oxide and carbon dioxide. The advantages and disadvantages of different cryogens and cryosurgical instruments are important considerations in their selection for specific ophthalmic applications
- Cryotherapy affects a sphere of tissue within a radius extending from the application device

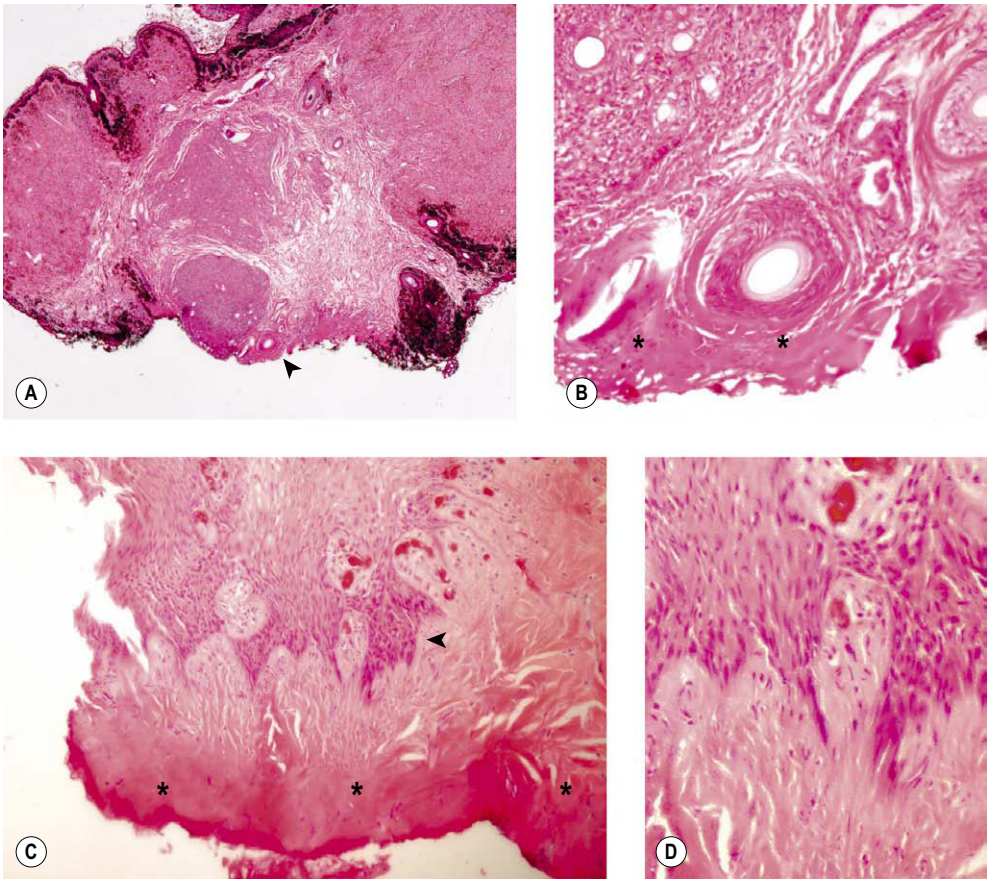


Figure 4.14 Tissue artifacts resulting from electrocautery. (A,B) Low magnification photomicrograph (A) and higher magnification (B), of the area by the arrow, show coagulated tissue (*) typical of electrocautery. (C,D) Low magnification photomicrograph (C) showing electrocautery burn similar to (A) and (B) (*). The higher magnification photomicrograph (D) showing, from the area near the arrow, the stretching effect of electrocautery on epithelial cells.

- The radius of the ice ball generated and the rate of freezing is diminished in highly vascular tissues because the flow of blood moderates the temperature of the tissues. Pigmentation does not significantly influence tissue cryobiology
- Freezing causes cell lysis, cellular dehydration and thermal shock with ischemic/and coagulation necrosis, with subsequent removal of the affected cellular components. Freezing has little effect on the qualitative nature of the connective tissues, such as the sclera. Eventually stromal elements and epithelium may 'grow back', but return of more complex tissue organization is incomplete
- The acute effects of cryotherapy are tissue edema and necrosis which stimulates a granulation tissue response
- The end effects are atrophy and disorganization of the affected tissues.

The effects of surgical laser (Figs 4.15, 4.16)

Diode lasers

- Penetrate deeply into the tissues until preferentially absorbed by pigmented tissue, when their energy is converted to heat
- May be delivered through the clear cornea without causing significant damage to the corneal endothelium
- Morphologic consequences of diode laser use:
  - The effect occurs by thermal coagulation of tissues within a certain radius of where the heat energy is generated (usually pigmented tissue)
  - Collagen is affected by a coagulation reaction much like electrocautery
  - Cellular tissues undergo coagulation necrosis followed by resorption
  - With time, stromal tissue might reform, but complex elements of tissue reorganization do not occur. The end result is an atrophic scar
- Uses of diode lasers
  - Cyclophotocoagulation for glaucoma (Fig. 4.15) transscleral or endoscopic delivery of laser energy is used to elicit focal ablation of ciliary body tissue
    - The goal of cyclophotocoagulation is to destroy the aqueous-producing ciliary body epithelium
    - The effects of cyclophotocoagulation are different in dogs with brown versus blue irides:
      - In heavily pigmented dogs, much of the energy is absorbed by, and destroys, the pigmented tissues of ciliary stroma just inside the sclera. This results in necrosis and ablation of pigmented stroma, inner sclera, ciliary nerves, blood vessels, and ciliary muscles, but not ciliary epithelium
      - In blue-eyed dogs, the light energy passes through the non-pigmented sclera and ciliary stroma and is absorbed directly by the pigmented ciliary epithelium, creating a local ablation which is more focused on the target tissue
  - Retinopexy (Fig. 4.16)
    - Transpupillary or transscleral delivery typically used for this application in veterinary patients
    - Lesions produced are inconsistent, due to variations in pigmentation of the ocular fundus in dogs, particularly in tapetal region

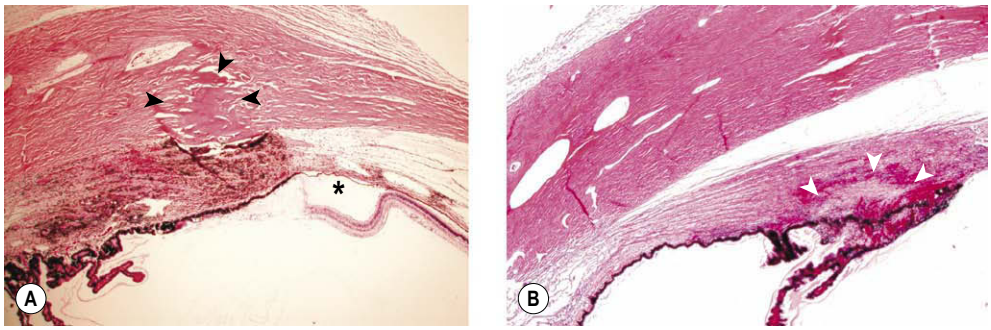


Figure 4.15 Laser retinopexy. Gross photograph of a canine globe, taken immediately after surgery, showing laser retinopexy sites.

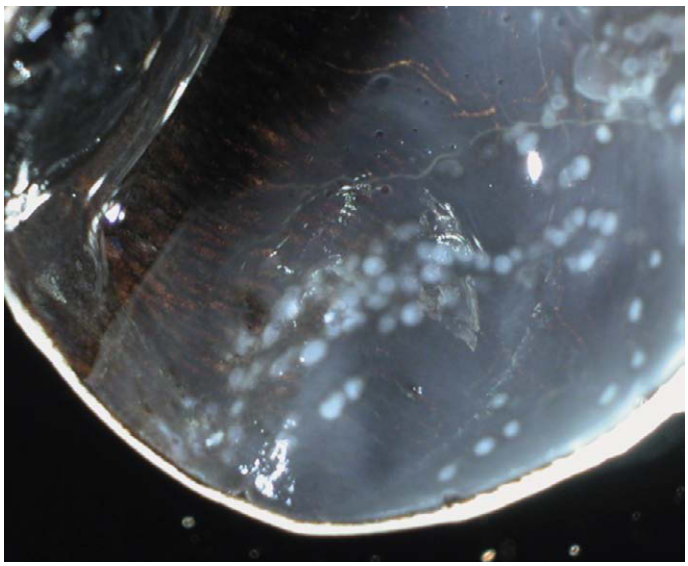


Figure 4.16 Transscleral laser cyclophotocoagulation. (A) Photomicrograph showing transscleral laser cyclophotocoagulation in a dog with a pigmented ciliary body. The cauterized tissue is centered on the inner sclera adjacent to the first pigmented tissue in the lasered field (black arrows). (B) Photomicrograph showing transscleral cyclophotoablation in a blue-eyed dog. The cauterized tissue is around the pigmented epithelial cells. The laser energy is converted to heat by the melanin pigment of the ciliary epithelium (white arrows).

  - By the transpupillary route, optimal energy delivery is characterized by outer retinal necrosis and RPE migration, with minimal gliosis or inflammation. Excessive energy settings may be associated with pan-retinal and choroidal necrosis, and with focal retinal detachment
  - Transscleral delivery is associated with mild perivascular scleritis and scleral thinning, choroidal thinning and variable retinal degeneration with RPE migration
- Ablation of pigmented mass lesions
  - Ablation of epibulbar and iris melanoma
  - Rupture of pigmented uveal cysts
  - Treatment of hypertrophic and cystic corpora nigra in horses
  - The corneal endothelium may sustain localized damage as a result of thermal energy released by the treated pigmented masses.

CO_2 laser

- Less commonly used in veterinary ophthalmology
- Does not penetrate tissues
- Used to create a controlled surgical ablation of surface tissues, this application has been applied to the management of corneal squamous cell carcinoma and eyelid neoplasia in veterinary patients
- The characteristic morphologic change is a narrow line of coagulated collagen seen at the incision site.

Nd:YAG laser

- For cyclophotoablation in the management of canine glaucoma
  - Cataract formation appears to be a more common complication following cyclophotoablation with Nd:YAG, than with diode laser
- For the ablation of pigmented mass lesions
- Used in the Q-switched mode, the Nd:YAG laser has a photodisruptive tissue effect that has been used for:
  - Laser posterior capsulotomies in the treatment of lens capsular opacities following cataract surgery
  - Iridotomies, synechiotomies and sclerostomies
  - For the rupture of pigmented uveal cysts
  - Treatment of cystic corpora nigra in horses.

Photodynamic therapy

Photodynamic therapy makes use of light energy combined with chemical photosensitive agents which amplify the tissue effect. If the photosensitive agent is administered intravascularly the light-induced effect will center on blood vessels potentially destroying the blood supply to a neoplasm. Since less light energy is used and the damage is more localized the morphologic affects are limited.

Comparative Comments

Few complications are encountered in humans as a result of electrocautery, cryoapplication, or surgical laser treatment.

Lens surgery

Surgery to remove the lens in cases of lens luxation:

There are 42 canine globes in the COPLOW collection that were enucleated following surgery to remove the lens.

- Relatively common complications are related to:
  - Integrity of the surgical wound
    - There are seven cases of corneal perforation
  - Postoperative inflammation (uveitis or endophthalmitis)
    - There are 22 cases of severe inflammation in the COPLOW collection
  - Attenuation of the corneal endothelium, resulting in corneal edema, that may reflect pre-existing trauma by contact with

an anteriorly luxated lens, or as a result of endothelial touch during intraocular surgery (as discussed above)

- Anterior prolapse of the destabilized, and often degenerate, vitreous may contribute to:
  - Glaucoma
  - Retinal detachment, related to vitreous traction.

Phacoemulsification or manual extracapsular extraction surgery for cataract (Figs 4.17, 4.18)

There are 117 cases of globes removed following cataract surgery in the COPLOW collection, 113 in dogs and four in cats.

- In cataract surgery patients, non-specific complications of intraocular surgery relate to:
  - The integrity and healing of the surgical wound
  - Inflammation (that may reflect exacerbation of pre-existing lens-induced uveitis, or endophthalmitis related to intraoperative contamination)
  - Attenuation of the corneal endothelium (see above)
  - The formation of intra-vitreal traction bands, leading to retinal detachment
  - Formation of pre-iridal fibrovascular membranes and neo-vascular glaucoma (see above)
- Complications directly associated with metaplasia, proliferation, and migration of lens epithelial cells after phacoemulsification, or manual extracapsular, cataract surgery include:
  - Lens epithelial cell metaplasia
    - The cell undergoes a transformation to a mesenchymal, spindle cell/myofibroblast-like morphology, with extracellular collagen deposition
    - With time, the metaplastic cells 'disappear', and only the collagen remains
  - Lens epithelial cell proliferation
    - Proliferating cells remain attached to the lens capsule, but they can form pronounced nodules of spindle cells
  - Lens epithelial cell migration after cataract surgery
    - Residual lens epithelial cells remaining after cataract surgery can migrate to the posterior capsule, leading to posterior capsular opacification
      - This complication is less likely to occur if a prosthetic intraocular lens is inserted into the capsular bag, and is influenced by the material from which the prosthetic lens is manufactured, as well as the lens design
    - Lens epithelial cells can also migrate outside the lens capsule
      - These cells continue to remain attached to tissue surface. They can cause pre-iridal membranes and, particularly when there is evidence of posterior lens capsule rupture, can incorporate the ciliary processes or extend across the anterior vitreous face. These lens epithelial cell membranes can contribute to traction bands leading to retinal detachment
    - Lens epithelial migration and proliferation outside the capsular bag rarely happens in human globes but is seen

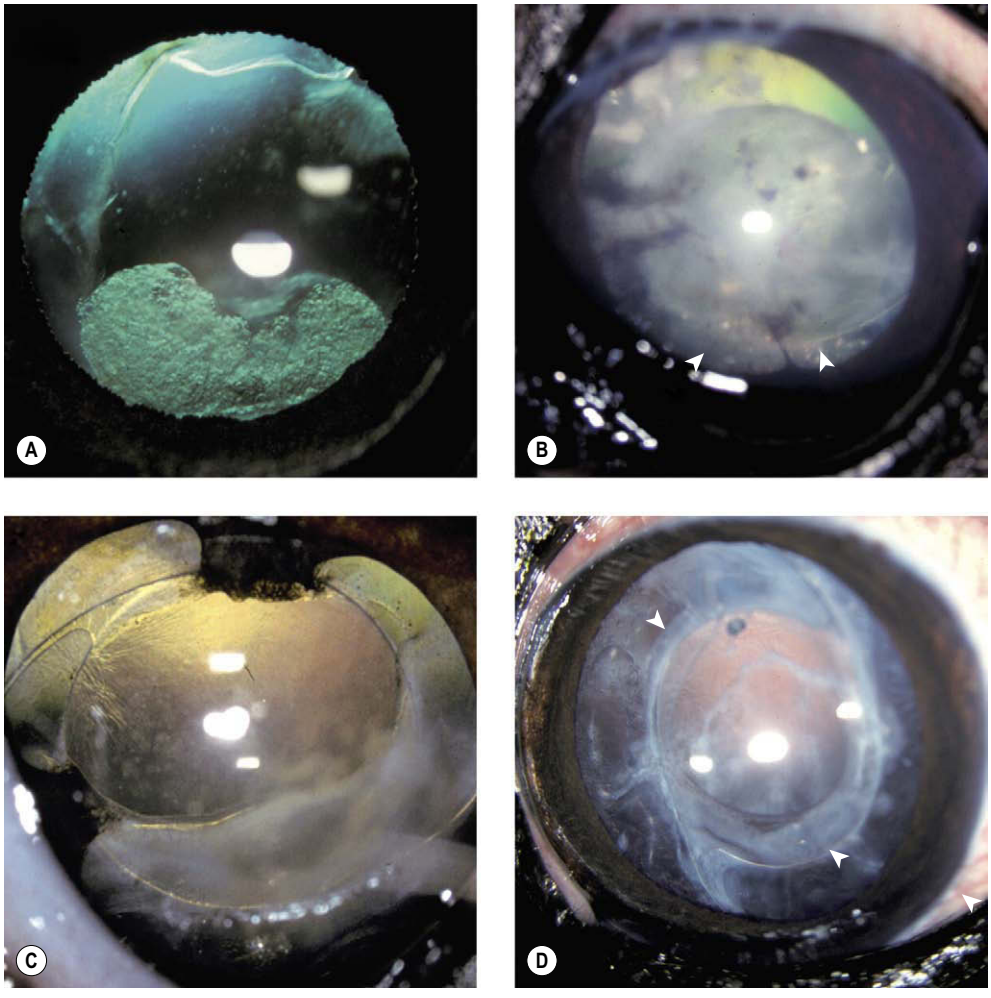


Figure 4.17 Elschnig's pearls, capsular opacities. (A) Labrador Retriever cross, 5 years old: a large area of Elschnig's pearls can be seen. (B) German Shepherd Dog, 11 years old: Elschnig's pearls are present at the arrows. Severe capsular opacities are also present. (C) Old English Sheepdog, 8 years old: anterior and posterior capsular opacities are present inferiorly. (D) Boston Terrier, 7 years old: the arrows point to the margins of the intraocular lens (IOL). Diffuse capsule opacities reduce the tapetal reflex.

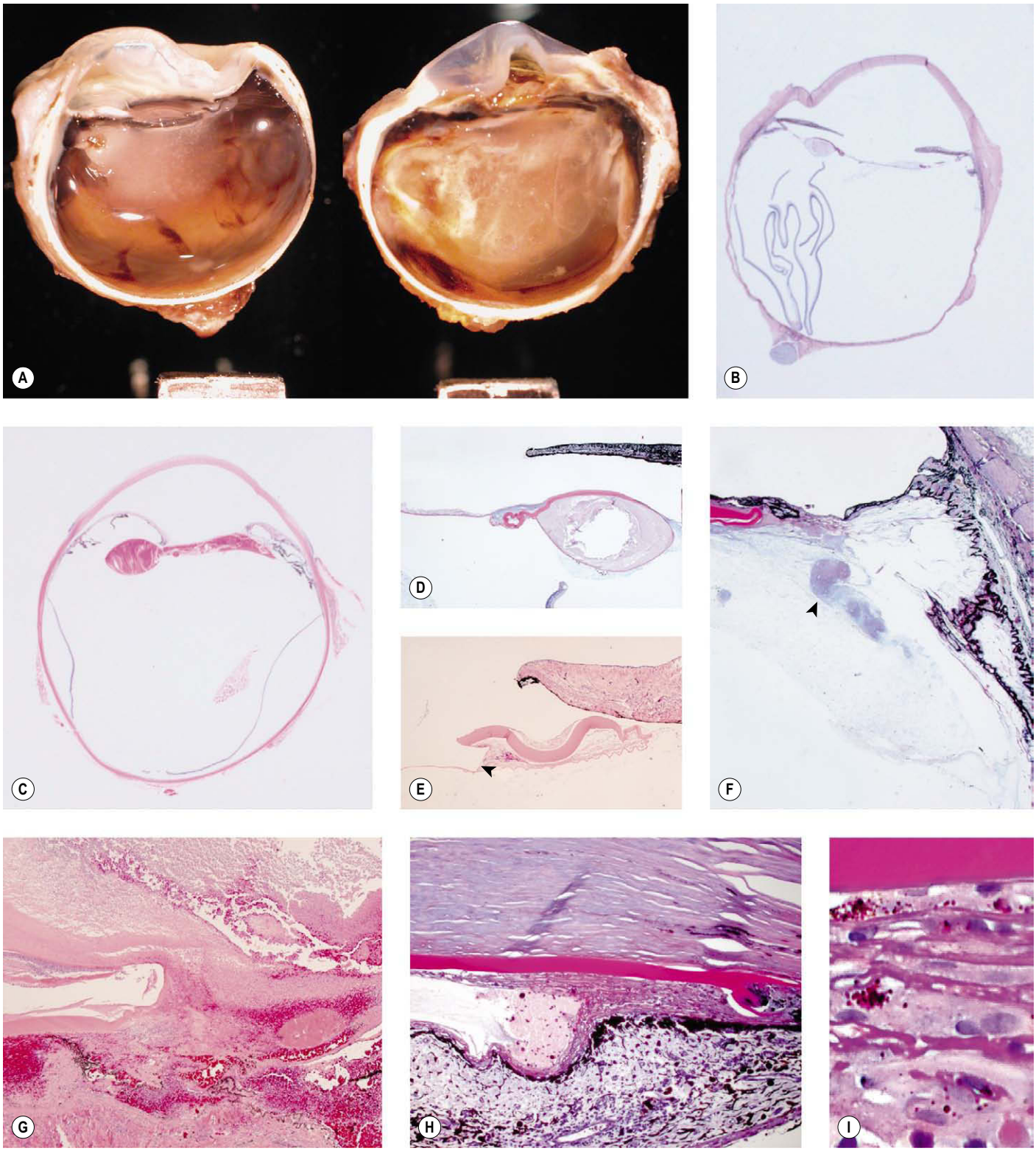


Figure 4.18 Cataract surgery complications, pathology. (A) Gross photograph showing both globes from a dog with postoperative endophthalmitis following cataract surgery. (B) Subgross photomicrograph of a canine globe with complete retinal detachment and giant retinal tear associated with traction from spindle cell membranes attached to the lens capsular bag. (C) Subgross photomicrograph of a rabbit globe showing extensive lens fiber re-growth. (D) Lens fiber re-growth in the capsular bag of a dog eye. (E) Collagen both inside and outside of the capsular bag in a dog eye. The squared-off empty space (arrow) outlines where the foldable IOL was positioned. (F) Photomicrograph of a canine globe with extensive cyclitic membrane and a traction band on the anterior vitreous (arrow). (G) Extensive fibroblast proliferation as well as hemorrhage around the lens capsule. The roughly rectangular empty space is where the foldable IOL was in place. (H,I) Photomicrographs showing lens epithelial cells characterized by PAS-positive basement membranes surrounding individual cells. The cells have migrated into the anterior chamber and are associated with a broad anterior synechia.

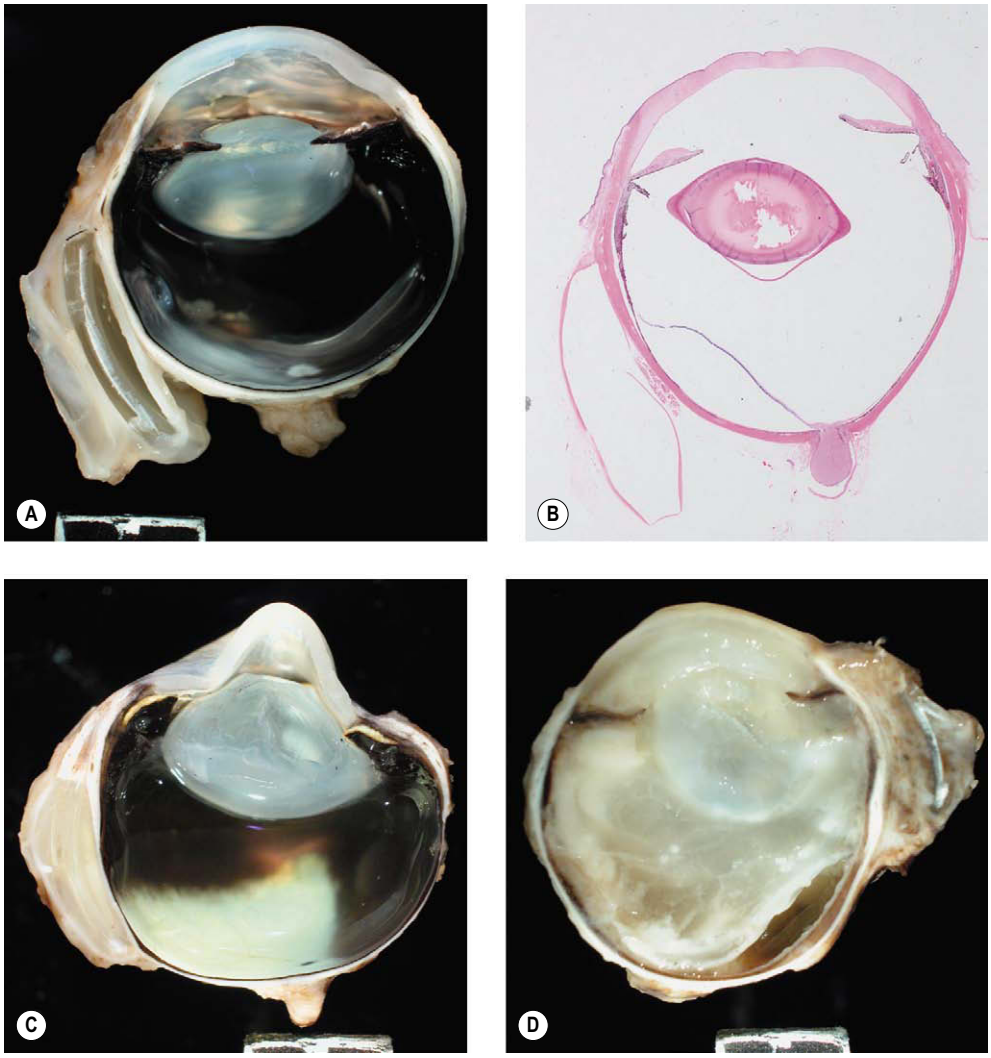


Figure 4.19 Glaucoma drainage implant. (A,B) Gross photograph and subgross photomicrograph showing a canine globe with an intact Ahmed valve device used to treat glaucoma. The device is designed to create a subconjunctival reservoir around the implant. Drainage into the reservoir is by way of a tube inserted into the anterior chamber. (C) Gross photograph of a feline globe similar to (A). (D) Gross photograph of a canine globe with endophthalmitis from infection spreading via the implant.

in both dogs and cats after surgical or spontaneous trauma (see Ch. 5)
  - Cataract 're-growth' secondary to lens epithelial proliferation and lens fiber differentiation may occur (Elschnig's pearls and Soemmerring's ring cataract)
- There are only four cats in the COPLOW collection whose eyes were removed after cataract surgery, however, two of the four had feline post-traumatic ocular sarcoma, spindle cell variant (see Ch. 5).

Comparative Comments

Cataract surgery is the most commonly performed surgical procedure of any type in humans, and lens epithelial proliferation and migration are commonly encountered but rarely contribute to loss of the eye.

Glaucoma drainage implant surgery (Fig. 4.19)

- Globes may be enucleated after drainage implant placement because of surgical or mechanical complications contributing to failure of the procedure
- The intent of the surgical procedure is to provide an alternate route for the drainage of aqueous from the anterior chamber. This is accomplished by placement of a device which consists of a narrow tube implanted into the anterior chamber, through which aqueous humor typically drains into a subconjunctival bleb, or reservoir, from which it is absorbed into the circulation. This sub-conjunctival reservoir is generally maintained by a variably shaped plate that is anchored to the sclera. Alternate routes for aqueous drainage from anterior chamber implants include the frontal sinus
- Cyclo-destructive procedures such as transscleral or endoscopic laser cyclophotocoagulation or cyclocryotherapy (as discussed previously) may be combined with, precede, or follow drainage implant surgery, and will contribute to pathological findings in subsequently enucleated globes

Comparative Comments

Lens epithelial migration and proliferation outside the capsular bag rarely happens in human globes.

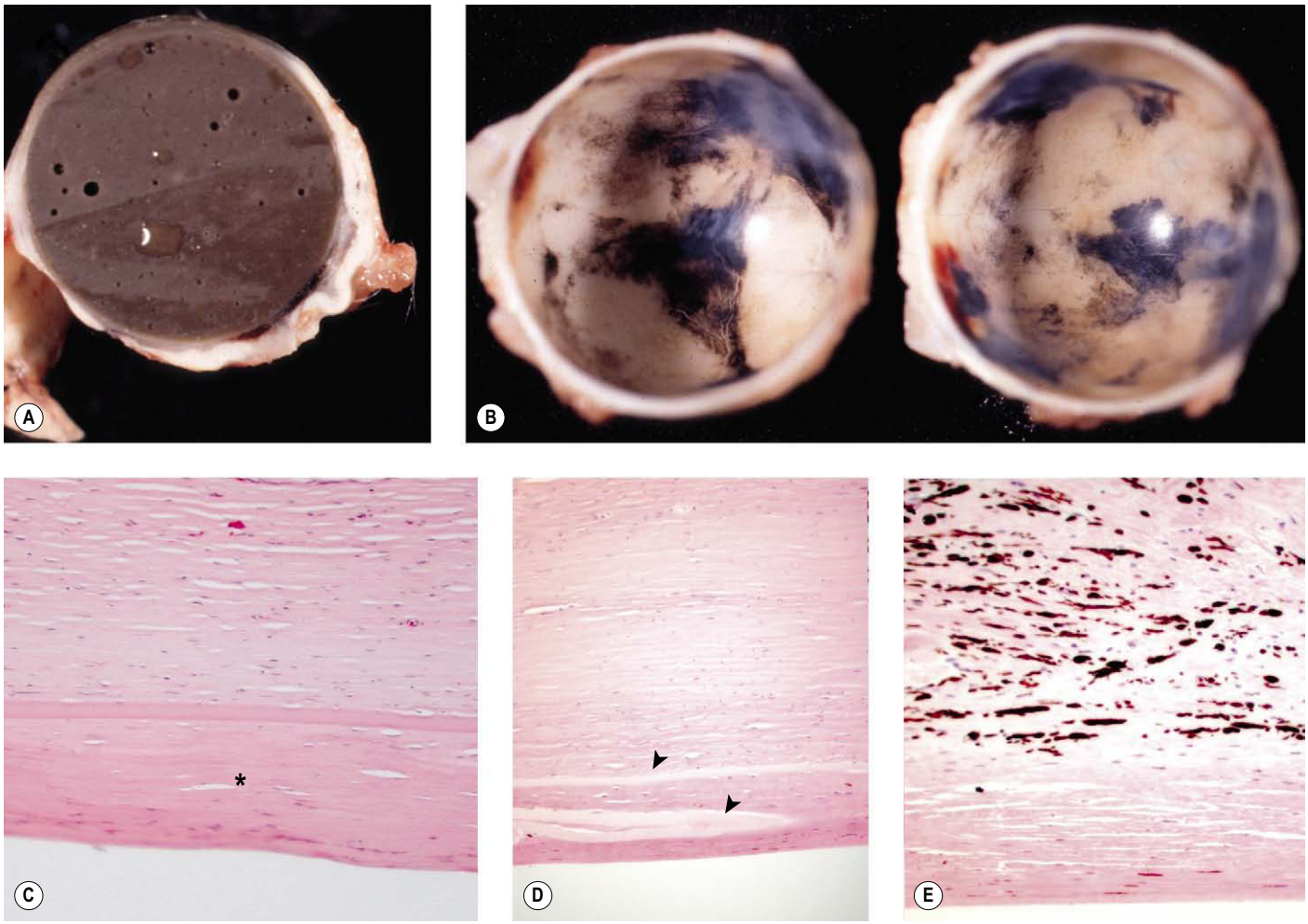


Figure 4.20 Uncomplicated intrascleral prosthesis. (A) Gross photograph of silicon rubber implant still in the scleral shell. (B) The same globe as (A), photographed after removing the prosthesis. (C,D) Photomicrographs of the posterior cornea show an avascular collagen-rich membrane (*) internal to Descemet's membrane. The arrows show fragments of Descemet's membrane. (E) Photomicrograph showing a similar membrane internal to remaining pigmented uveal tissue in the posterior segment.

- Implant failure is often associated with the formation of fibrin or, ultimately, scar tissue, which obstructs the capillary effect of the anterior chamber tube, or results in obliteration of the filtering bleb
  - A great deal of effort may be required on the part of the pathologist to obtain sections required to determine the cause of implant failure, particularly if the location of the device is not marked on the enucleated globe
- Other relatively common postoperative complications include inflammation, dehiscence of the implant or conjunctival incision, epithelial growth into the reservoir, cataract, and corneal endothelial attenuation.

Comparative Comments

Complications from glaucoma valve surgery in humans parallel those seen in animal eyes.

Intrascleral prostheses and evisceration surgery (Figs 4.20–4.22)

Evisceration with intrascleral prosthesis placement is a common surgical alternative to enucleation in the management of severe, untreatable ocular disease in veterinary patients. The most common indication for evisceration is intractable glaucoma in an irreversibly blind eye.

Advantages

Advantages of evisceration and intrascleral prosthesis over enucleation include:

- The superior cosmetic outcome
- Many owners express a psychological hostility to the removal of the eye and this procedure seems to offer what seems like a more acceptable compromise.

Disadvantages

Disadvantages of evisceration and intrascleral prosthesis over enucleation include:

- Complexity of surgical procedure relative to enucleation
  - Usually done only by a specialist
  - Additional expense
- Suboptimal specimen available for pathological evaluation
- Corneal health is a significant postoperative concern, affecting patient comfort, the ability of the corneoscleral shell to retain a prosthesis and the cosmetic outcome
- If the intrascleral prosthesis fails, a second surgical procedure is required, with the possibility of attendant complications that might adversely affect the health of the animal.

Reasons for corneoscleral shell failure, from the perspective of the COPLOW archive, are consistent with previously published reports (see references), and include:

- Dogs: 1448 evisceration specimens and 60 corneoscleral shell/intrascleral prosthesis failures submitted (4.1%)
  - 38 of 60 cases: inflammatory disease, including severe inflammation within the corneoscleral shell, with or without epithelial down-growth (11 cases) (Fig. 4.21)
  - 22 of 60 cases: re-growth of neoplasm
    - Of 1448 evisceration specimens, a diagnosis of neoplasia was made in 146 (10%) (Fig. 4.22)
    - All but two of the 22 cases with intrascleral prosthesis failure related to recurrence of neoplasia involved malignant tumors
  - 13 of 60 cases: failure of the corneoscleral shell, including wound dehiscence, severe keratitis, corneal abscessation, and one case with a corneal stromal cyst
- Cats: 76 eviscerations and 11 corneoscleral shell/intrascleral prosthesis failures (14.5%)
  - 2 of 11 cases: inflammatory disease within the corneoscleral shell
  - 9 of 11 cases: re-growth of malignant neoplasia
    - 17 evisceration samples had tumors (22.4%).

Our experience highlights the importance of appropriate case selection for evisceration with intrascleral prosthesis placement:

- Evisceration does not represent a good option in cats
  - The ratio of corneoscleral shell failures to evisceration samples in the COPLOW collection is 14.5%

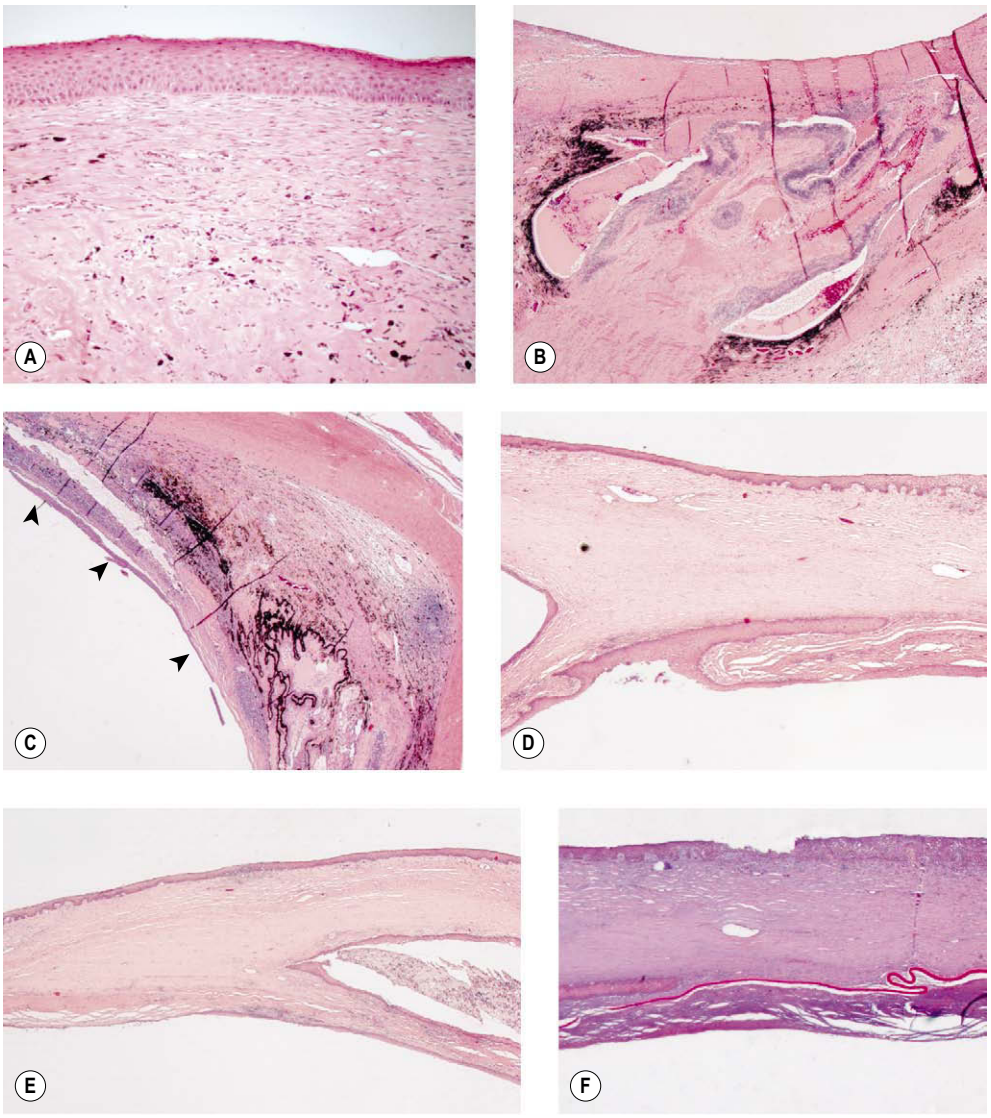


Figure 4.21 Corneoscleral shell failure. (A) Photomicrograph showing extensive stromal keratitis, which may predispose to scleral shell failure or be the cause of failure. (B) Photomicrograph of a canine corneoscleral shell showing retained choroid and retinal tissue entrapped by the typical collagen-rich membrane. (C) Photomicrograph showing epithelial down-growth (arrows) forming defects in the corneal stroma and filling the inner aspect of the corneoscleral shell. There is also an excessive amount of retained ciliary body tissue. (D,E) Photomicrographs showing epithelial down-growth, both within the corneal stroma and filling the inner lining of the scleral shell. (F) Photomicrograph showing extensive corneal stromal fibrosis, ulcerative keratitis and a thick collagen-rich membrane on the inner cornea (Alcian blue PAS).

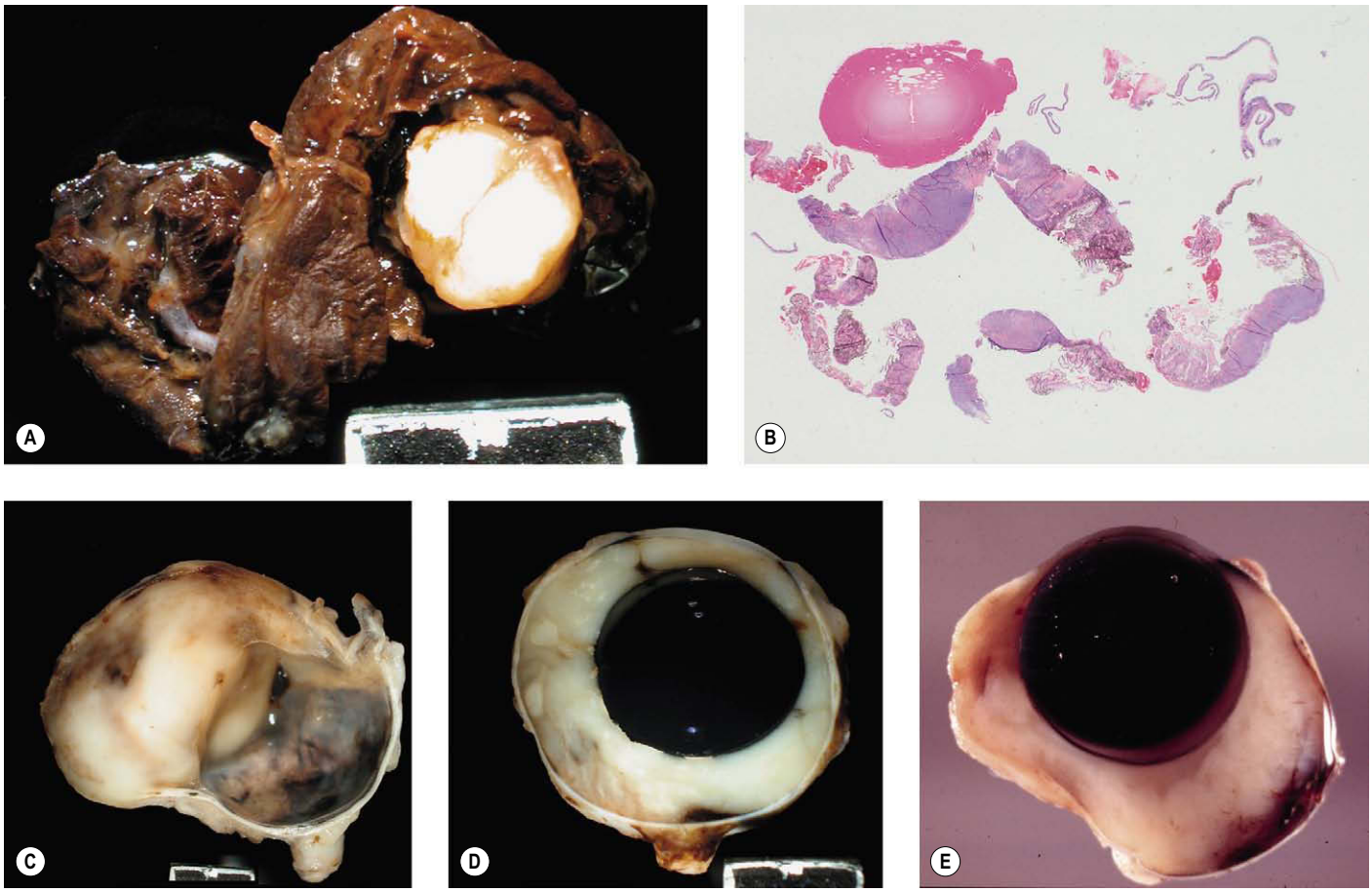


Figure 4.22 Neoplasia and evisceration with intrascleral prosthesis. (A) Gross photograph of an evisceration specimen containing a nodular white neoplasm (canine iridociliary adenoma). (B) Subgross photomicrograph of an evisceration specimen showing a basophilic neoplasm (canine malignant melanoma). (C–E) Three gross photographs showing re-growth of neoplastic tissue within the corneoscleral shell. (C) Canine spindle cell tumor of blue-eyed dogs; (D) feline lymphoma; (E) amelanotic feline diffuse iris melanoma.

  - Of corneoscleral shell failures, 82% were due to the re-growth of malignant tumors, with life-threatening potential
- Evisceration with intrascleral prosthesis is a reasonable option in dogs with a history of a well-defined ocular disease like primary glaucoma with confirmed goniodysgenesis. The procedure may also be considered in dogs where a thorough ocular exam, in combination with other clinical diagnostic findings, can essentially rule out neoplasia or severe, active intraocular inflammation
- Evisceration with intrascleral prosthesis is not a good option in dogs with conditions precluding a thorough ocular exam and making it ostensibly impossible to clinically rule out neoplasia or significant, active intraocular inflammation
- Caution should be exercised when considering this procedure in dogs with suspected intraocular neoplasia, or with pre-existing corneal disease, or other disease that may compromise the integrity or healing of the corneoscleral shell.

Common lesions observed in corneoscleral shells submitted from animals that had intrascleral prostheses include:

- Stromal keratitis
  - Most corneoscleral shells submitted had some degree of corneal vascular infiltrate
- Retrocorneal membrane
  - The corneal endothelium was absent from almost every corneoscleral shell examined
  - The endothelium is replaced by an avascular, lamellar, collagen rich, spindle cell membrane that is not only adjacent to the cornea, but lines the interior of the globe
  - Remnant uveal tissue
    - Most corneoscleral shells examined contained some remnant uveal tissue
    - The remnant uveal tissue does not seem to have a major, adverse effect on postoperative outcome
    - Perhaps surprisingly, these uveal tissue remnants do not undergo fibrosis.

Comparative Comments

The most serious complications following evisceration surgery in humans are the development of sympathetic ophthalmia, an entity limited to humans, and the return or extension of a previously unrecognized tumor. Otherwise, problems following intrascleral prostheses and evisceration are similar to those described for animal eyes.

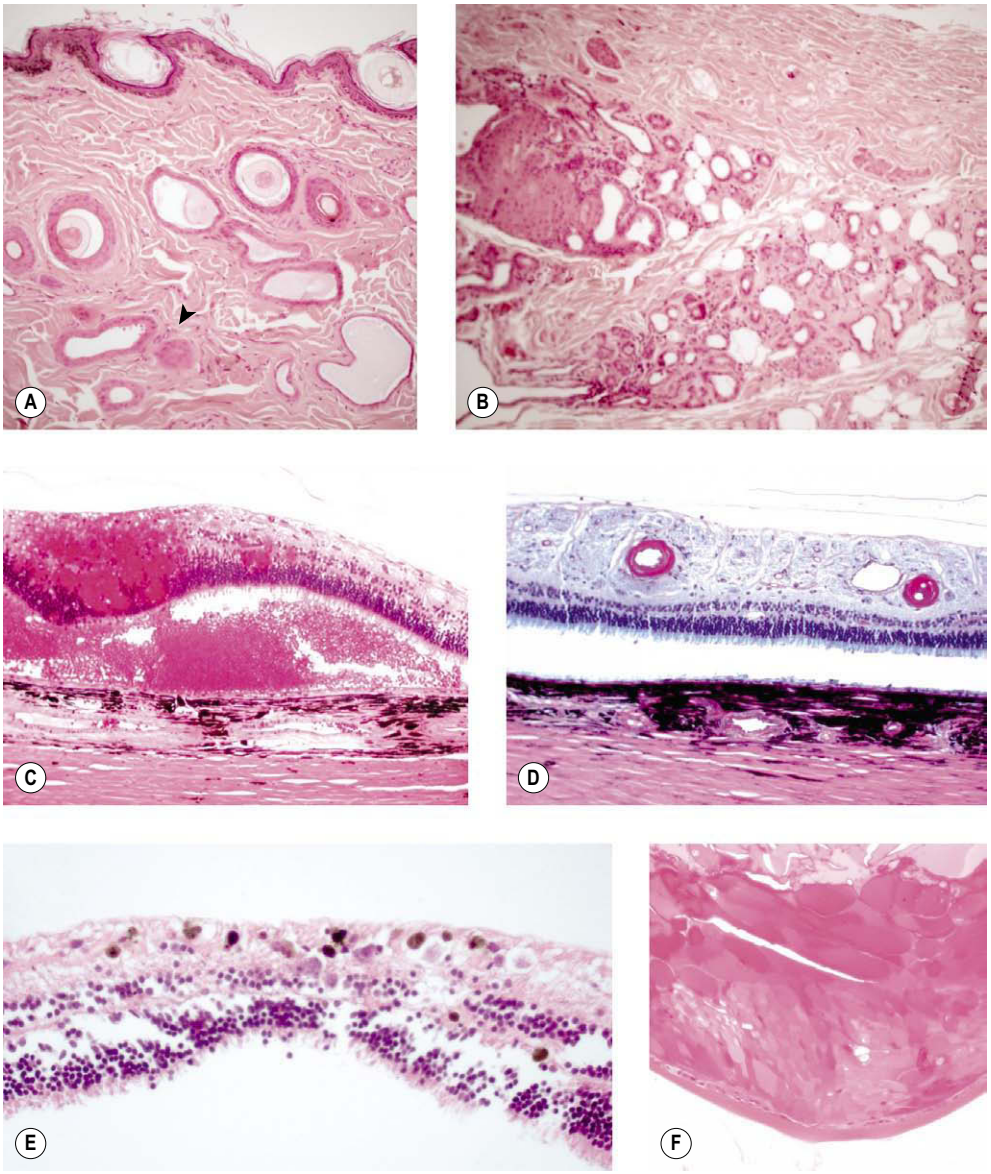


Figure 4.23 Radiation-induced lesions. (A) Photomicrograph of the eyelid skin from a dog with a history of radiation therapy showing follicular atrophy (arrow). (B) Atrophy of the gland of the third eyelid in a dog following radiation therapy. (C) Retinal and subretinal hemorrhage in a dog following radiation therapy. (D) Retinal vascular damage in a canine retina resulted from previous radiation therapy. (E) Retinal hemosiderophage accumulation in a dog with a history of radiation therapy. (F) Cataract in a dog attributed to previous radiation therapy.

Ocular complications following radiotherapy where the eye is in the irradiation field (Fig. 4.23)

Eyelid margin and haired skin of the eyelid

- Necrosis followed by atrophy of the pilosebaceous unit
- Vasculopathy
- Atrophy of the Meibomian glands, contributing to ocular surface disease (keratoconjunctivitis).

Lacrimal or nictitans glands

- Necrosis followed by atrophy
- Can be responsible for reduced tear production, leading to signs of keratoconjunctivitis sicca.

Lens

- Necrosis of the proliferative layer of the lens epithelial cells leads to equatorial cortical cataract.

Retina

- Retinal vasculopathy is recognized as a relatively common, chronic, long-term adverse effect:
  - Retinal hemorrhage
  - Retinal edema
  - Regional retinal ischemia.

Comparative Comments

Ocular complications of radiation therapy in humans, in which the eye is in the irradiation field, usually involve retinal vasculopathy, although dry eye, loss of lashes and eyebrow, and chronic erythema are all encountered.

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Chapter 5

Non-surgical trauma

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THE RELATIVE IMPORTANCE OF OCULAR TRAUMA IN A MAIL-IN PATHOLOGY PRACTICE

The relative importance of non-surgical trauma is hard to estimate:

- It is the third most common reason for enucleation in dogs and cats, behind glaucoma and neoplasia
- It is estimated that 20% of canine submissions to COPLOW are related to non-surgical trauma.

Comparative Comments

Non-surgical trauma is the leading cause of enucleation in the experience of the University of Wisconsin Eye Pathology Laboratory. It is estimated that about 20% of the human eye submissions are related to non-surgical trauma.

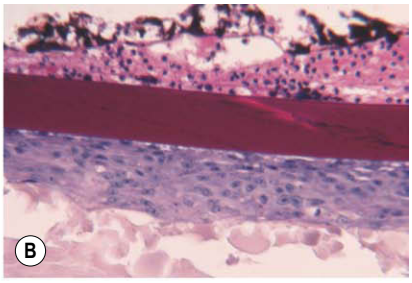
Yanoff and Fine (2002) state that trauma (both surgical and non-surgical combined) accounts for 35% of all enucleations.

GENERAL POST-TRAUMATIC RESPONSE OF OCULAR TISSUES, REGARDLESS OF THE TYPE OF TRAUMA

Non-specific proliferative reaction (Figs 5.1–5.3)

- Within a few hours of trauma, cellular proliferation may be recognized in the lens epithelium and the non-pigmented ciliary body epithelium (Fig. 5.1)
- After about 48 h of trauma, spindle cell and neovascular proliferation extend into the aqueous or vitreous compartments of the globe (Fig. 5.2) (see also Ch. 9)
  - Neovascular proliferation
    - May contribute to subsequent intraocular hemorrhage, potentially setting up a vicious cycle
  - Pre-iridal fibrovascular membrane
    - May lead to peripheral anterior synechiae that, in turn, contributes to the development of neovascular glaucoma





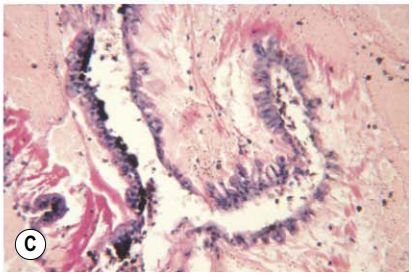
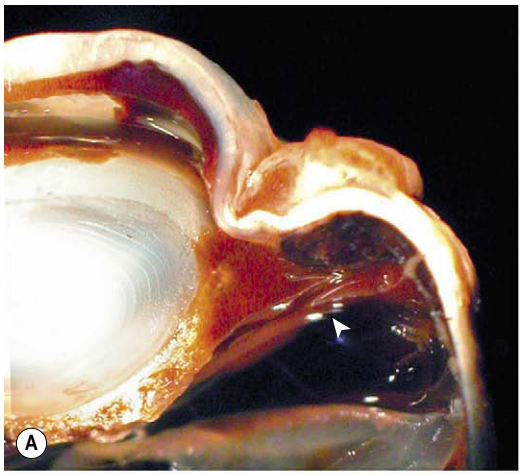
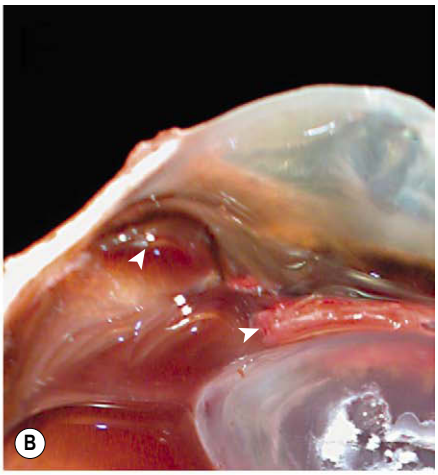


Figure 5.1 Cellular effects of trauma. (A) Gross photograph of a feline globe removed 3 h after blunt trauma showing lens capsule rupture and retinal tear. (B) Photomicrograph showing the lens capsule and lens epithelial cell proliferation and spindle cell metaplasia in a feline globe removed 8 h after a traumatic event. (C) Photomicrograph showing the non-pigmented ciliary epithelial cells proliferating in a canine globe removed 5 h after a traumatic event.





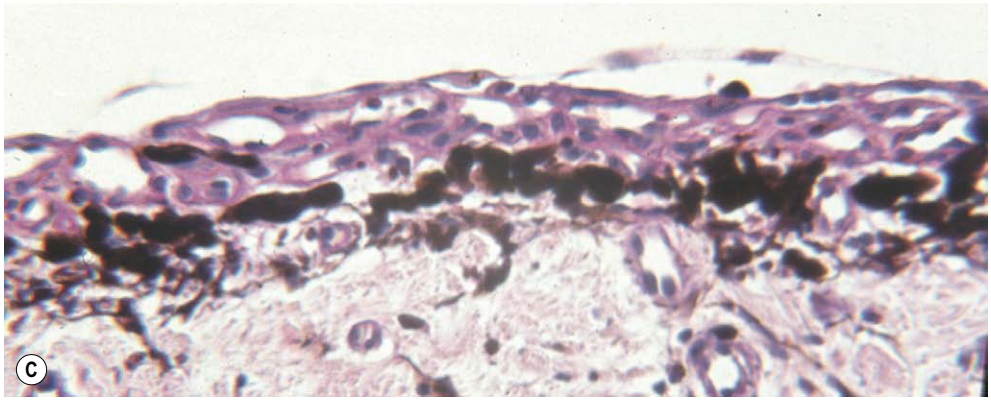


Figure 5.2 More cellular effects of trauma. (A) Gross photograph of a canine globe showing broad anterior synechiae and developing cyclitic membrane (arrow). (B) Gross photograph of a canine globe showing posterior synechia (arrows) and iris bombé. (C) Photomicrograph of the anterior surface of the iris showing a pre-iridal fibrovascular membrane in a canine globe after trauma.

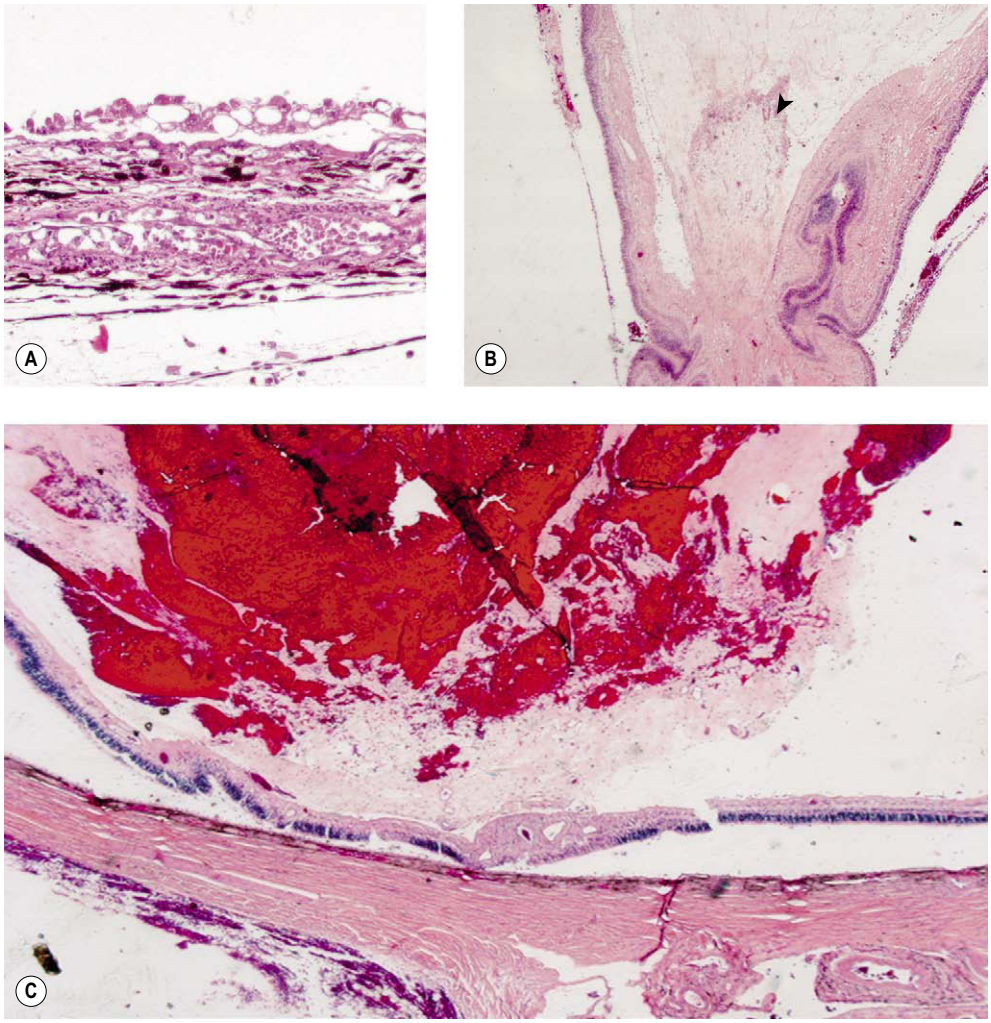


Figure 5.3 Fibrovascular proliferation in the globe. (A) Photomicrograph showing a choroidal neovascular proliferation in a traumatized canine globe. (B) Photomicrograph showing a fibrovascular membrane extending from the optic nerve head into the vitreous body in a traumatized dog globe (arrow). (C) Low magnification photomicrograph of a canine globe showing extensive intravitreal hemorrhage and neovascular proliferation near the optic nerve head.

- Posterior iridal neovascular membrane
  - Which may lead to posterior synechiae
- Cyclitic membrane
  - This can lead to traction resulting in retinal detachment
    - Retinal detachment and subsequent hypoxia leads to the release of growth factors which further stimulate neovascular proliferation
- Choroidal neovascular membranes (Fig. 5.3)
  - This can lead to subretinal hemorrhage or serous exudation, with subsequent retinal detachment
- Neovascular membranes extending from the optic disk into the vitreous in dogs
  - This can lead to traction and retinal detachment, with retinal hypoxia contributing to further neovascular proliferation
- Retinal neovascular membranes rarely occur in domestic animal species

Comparative Comments

Proliferative vitreoretinopathy occurs in humans secondary to trauma, or can be secondary to retinal detachment, and is rare in domestic species

- The general absence of granulation tissue formation within the tissues of the uveal tract is quite striking
  - If fibrosis is observed within the uvea, it is important to look for evidence of scleral rupture, which provides a portal for fibrosis originating within the episcleral tissues to enter the globe.

Comparative Comments

The post-traumatic reaction of ocular tissues described for animal eyes applies also for human eyes.

INTRAOCULAR HEMORRHAGE

Blood in the anterior chamber (hemophthalmos) (Fig. 5.4)

- May result from blunt or penetrating trauma, but has many other potential causes; including intraocular inflammation, neoplasia, fibrovascular membranes, retinal detachment, systemic hypertension or disorders of hemostasis

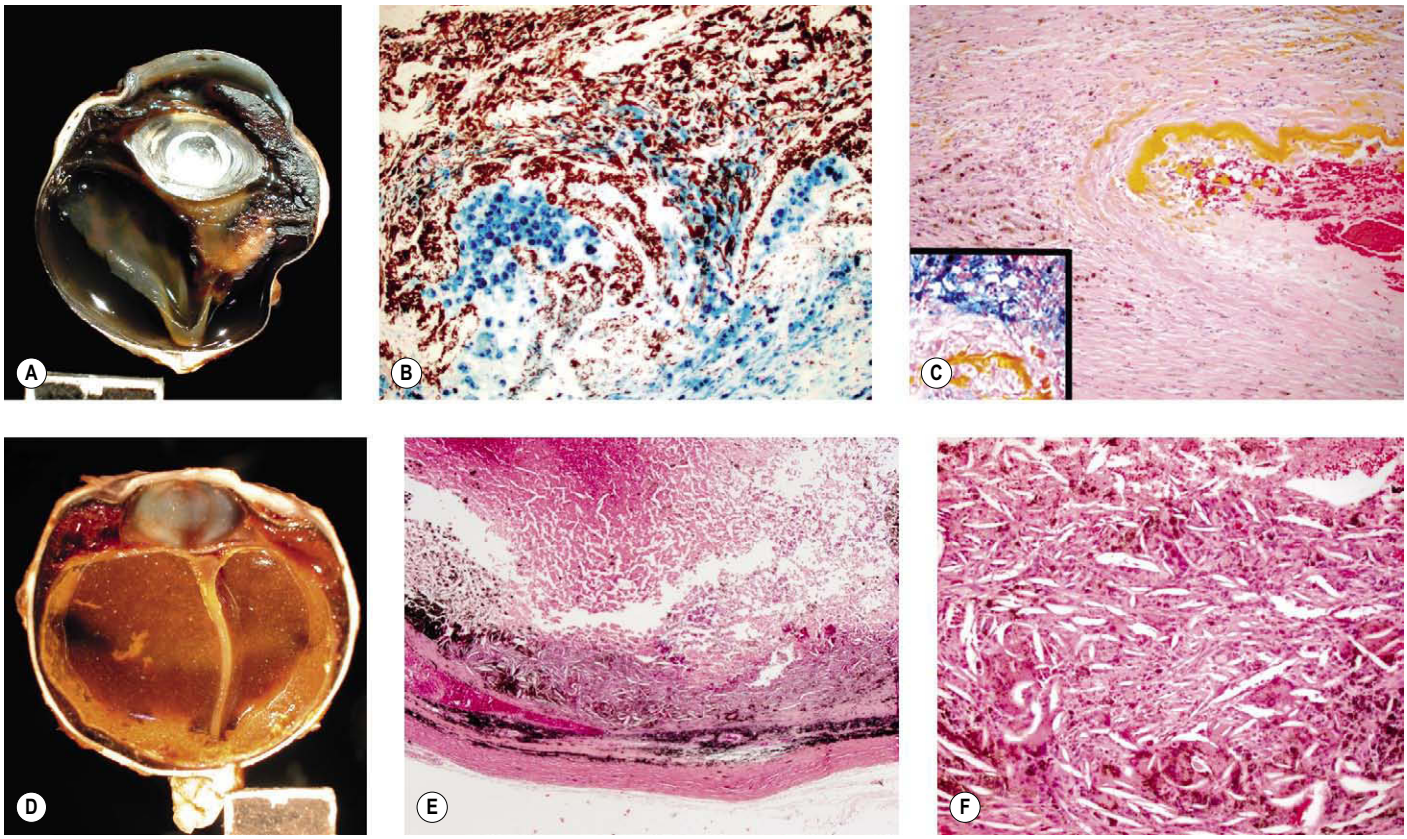


Figure 5.4 Effects of hemorrhage. (A) Gross photograph of a canine globe with retinal detachment and accumulation of blood pigments in a nodular lesion that distorts the peripheral retina and vitreous body. (B,C) Photomicrographs of the lesion in (A) show hemosiderin stained with Prussian blue in (B) and in the inset in (C). Yellow hematoidin pigment appears in (C). (D) Gross photograph of a canine globe with longstanding intraocular hemorrhage, hemosiderophage and cholesterol granuloma formation. (E,F) Low magnification and higher magnification photomicrographs, respectively of the same globe as (D), show a loose accumulation of macrophage cells and abundant cholesterol crystals indicated by the spindle-shaped empty spaces in (F).

- Hemophthalmos (blood in the anterior chamber) can contribute directly to the pathogenesis of glaucoma by obstructing conventional aqueous outflow via the drainage angle
- Hemophthalmos may play a role in stimulating a neo-vascular proliferative response which can lead to anterior or posterior synechiae, as well as predisposing to further episodes of intraocular hemorrhage
- In its aftermath, hemophthalmos can lead to secondary hemosiderosis
  - Blood pigment staining of the cornea, after traumatic hemorrhage, can involve hemoglobin, hemosiderin, or hematoidin. Staining is seen most often in the peripheral cornea and the tissues of the iridocorneal angle. A Prussian blue stain is useful to distinguish hemosiderin from melanin
- Continued hemorrhage can fill the globe (hemophthalmos)
  - Recurrent episodes of intraocular hemorrhage may reflect underlying disease; vicious cycles of hemorrhage associated with clotting and subsequent activation of the fibrinolytic pathway, or leakage from new vessels formed as part of a fibrovascular response
- *Cholesterolosis bulbi* (synchysis scintillans, cholesterol granuloma)
  - Blood which pools within the globe and is not resorbed will eventually be broken down to hemosiderin and cholesterol, stimulating a profound phagocytic response. Frequently, free cholesterol crystals are identifiable within the globe as acicular cholesterol clefts in tissues or free in the chambers of the globe. Cholesterol crystals are birefringent when viewed with polarized light, but only if the tissues are unprocessed.

Comparative Comments

The occurrence and sequelae of intraocular hemorrhages are little different in humans from those described in animal eyes.

NON-PENETRATING (BLUNT) OCULAR TRAUMA

Corneal effects

- Abrasion – not often a feature of a pathology submission
- Ruptures in Descemet's membrane
  - May lead to striate keratopathy
  - Relatively common clinical presentation in horses and may follow blunt trauma, such as whip or rope injuries to eye, although a history of trauma is often lacking
  - Careful evaluation is required to exclude glaucoma, which may cause of ruptures in Descemet's membrane related to globe stretching (see Ch. 13)

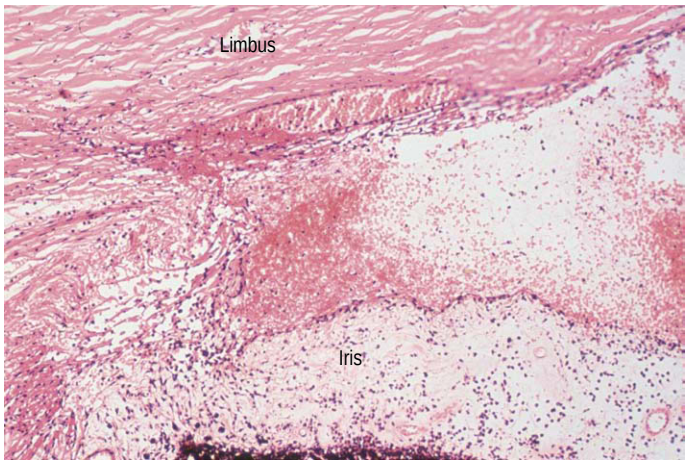


Figure 5.5 Acute cyclodialysis. Photomicrograph of a feline iridocorneal angle within hours of blunt trauma showing hemorrhage in the anterior chamber and iridocorneal angle, as well as tearing away of the iris and ciliary body from the sclera (cyclodialysis).

- Retrocorneal membrane; duplication of Descemet's membrane, and extension of Descemet's membrane over the iridocorneal angle:
  - These changes can be focal or diffuse and can be associated with corneal edema, causing corneal opacity
  - Traumatic changes to the endothelium and Descemet's membrane are characterized by the following:
    - Spindle cell metaplasia of the endothelium
    - Deposition of a cell-poor collagen posterior to the cornea even if the endothelium is still present
    - Duplication of Descemet's membrane
      - Most often the secondary Descemet's membrane is about the same thickness as the original
      - Multiple thin membranes are often seen
      - Extension of Descemet's membrane and extension of endothelium over the iridocorneal angle is sometimes seen.

Uveal effects (Figs 5.5, 5.6)

- Cyclodialysis, the tearing and separation of the ciliary body and iris base from the sclera creating an opening into the suprachoroidal space (Fig. 5.5)
  - Cyclodialysis is relatively more likely to occur in cats than dogs
    - This is because of the absence of a robust primary pectinate ligament structure in the feline iridocorneal angle
  - Cyclodialysis is relatively even more likely to occur in birds for the following reasons:
    - The rigid scleral ossicles of the avian eye magnify shearing forces, which act to strip the soft tissues of the ciliary body away from the sclera
    - The attachment apparatus at the iridocorneal angle is delicate
  - Cyclodialysis is recognized in the acutely traumatized eye by paying close attention to the loss of integrity of the ciliary cleft and the tissues around the ciliary cleft
    - However, years after the traumatic event, 'angle recession' may still be observed as evidence of prior trauma to the structures of the irido-corneal angle (Fig. 5.6)
- Angle recession is characterized by the dramatically increased distance between the end of Descemet's membrane and the anatomic irido-corneal angle. Angle recession has implications in aqueous drainage and is a risk factor in the development of glaucoma (see Ch. 13)
  - In some cases, Descemet's membrane extends over the inner sclera beyond the limbus and, in those cases, angle recession is recognized by the increased distance between the anatomic angle and the limbus.
- Rupture or avulsion of corpora nigra is often seen after blunt trauma in horses.

Lens effects (see also Ch. 10)

Cataract (Fig. 5.7)

Cataract is a common consequence of blunt trauma. Cataract can be prominent within days of trauma (Fig. 5.7).

- Anterior or posterior subcapsular cataract
- Cortical cataract, focal or complete, is often seen and it is good to search for other morphologic indicators of trauma such as retinal detachment or retinal necrosis/atrophy.

Lens capsule rupture (Figs 5.8–5.10)

Lens capsule rupture is a commonly observed consequence of non-penetrating injury to the globe, in submissions to the pathology laboratory.

Pathologic lens capsule rupture

Pathologic lens capsule rupture is differentiated from artifact by the following findings (in descending order of diagnostic value) (Fig. 5.8):

- Presence of inflammatory cells such as macrophages or neutrophils, or blood vessels, inside the lens capsule
  - This feature may be encountered, even if the actual lens capsule defect has not been sampled in the section
- Presence of a cellular reaction at the severed margins of the lens capsule
  - This reaction can involve proliferating lens epithelial cells, inflammatory cells, or spindle cells and may be associated with synechiae
- Recoil or scrolling of the severed ends of the lens capsule.

Inflammation

Inflammation (phacoclastic uveitis) is an important consequence of lens capsule rupture (Fig. 5.9).

- Immediately adjacent to the released lens material, there will be a foreign body granulomatous reaction
  - Some authors assert that lens proteins released following capsule rupture frequently elicit a robust pyogenic or pyogranulomatous response. However, one must be cautious in distinguishing the effects of sepsis; which would be expected to elicit a pyogenic reaction, and may be introduced by a penetrating injury; from the response induced solely by exposure of the lens proteins, which is typically a relatively 'bland' foreign body, granulomatous reaction
- Away from the immediate area of exposed lens protein, a lymphocytic and plasmacytic uveitis develops, that may be associated with synechiae or neovascular membrane formation
- Phacoclastic uveitis often results in secondary glaucoma, due to the formation of synechiae or neovascular membranes.

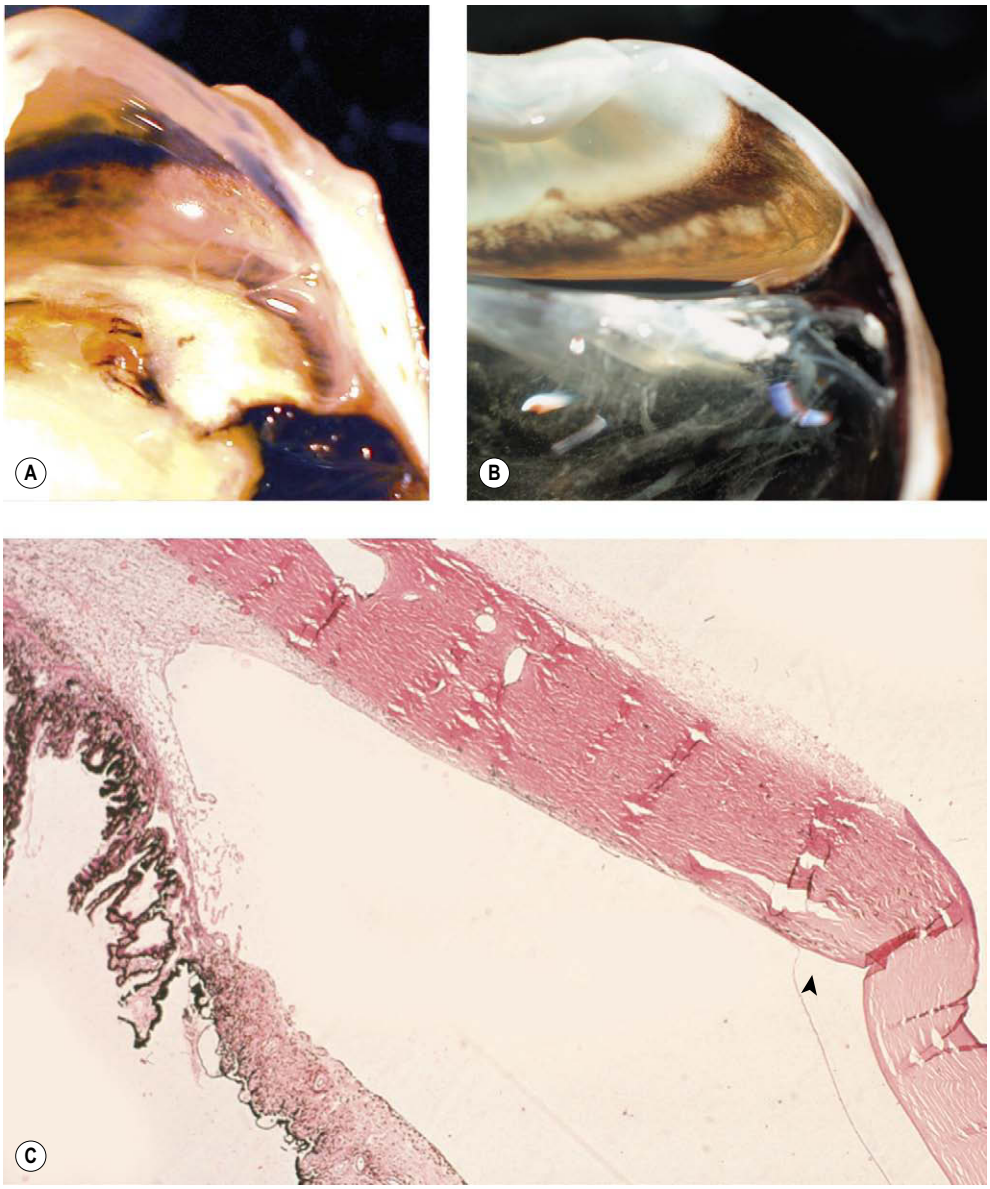


Figure 5.6 Iridocorneal angle recession. (A,B) Gross photographs of two feline globes show a wide space between the end of Descemet's membrane and the displaced iridocorneal angle (angle recession). (C) Low magnification photomicrograph of a feline globe showing an expanded distance between the end of Descemet's membrane (arrow) and the iridocorneal angle in angle recession.

Spindle cell metaplasia of lens epithelial cells and migration of lens epithelial cells (Fig. 5.10)

- Spindle cell metaplasia of lens epithelial cells is the first step in the formation of subcapsular cataract in response to trauma, and is associated with posterior capsular opacification after cataract surgery. It is an important feature of the intraocular reaction to lens capsule rupture in domestic animals
- Metaplastic lens epithelial cells express vimentin and smooth muscle actin, and they proliferate and migrate. They also produce collagen and secrete a thick basement membrane reminiscent of lens capsule
  - Lens epithelial cells of dogs and cats appear to have a greater tendency to proliferate and migrate in response to injury than those of humans
    - Metaplastic lens epithelial cells in damaged human lenses may migrate, but they seldom migrate away from the lens capsule
    - In dogs and cats, metaplastic lens epithelial cells often migrate along the surface topography of the inner aspect of the globe, including:
      - The outer surface of the lens
      - The anterior and posterior surfaces of the iris
      - The surfaces of the detached retina
      - The inner choroid, within the sub-retinal space
    - In cats, metaplastic lens epithelial cells may give rise to post-traumatic sarcoma
      - This neoplasm is discussed in detail later in this chapter.

Comparative Comments

A significant difference seen in the response to non-penetrating (blunt) ocular trauma in humans is a less aggressive spindle cell metaplasia and migration of lens epithelial cells after the lens capsule is ruptured.

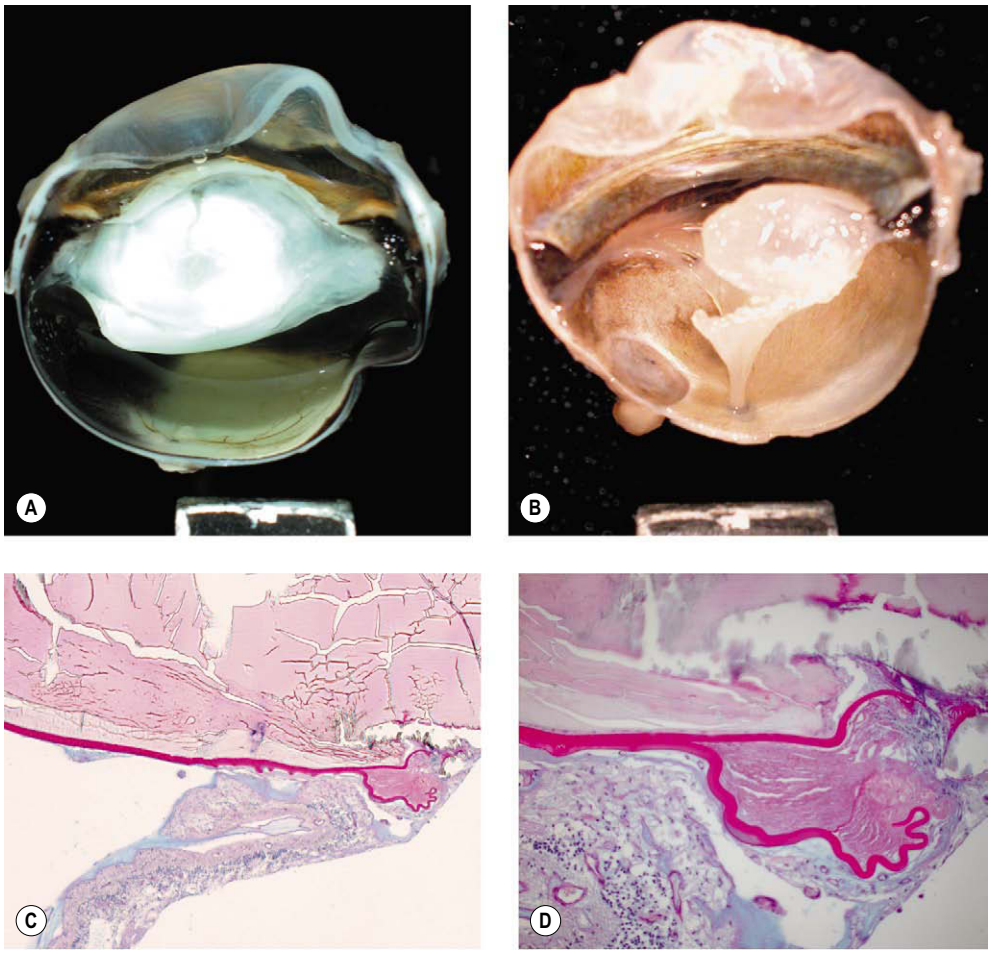


Figure 5.7 Traumatic cataract. (A,B) Gross photographs show trauma-induced cataracts in a cat (A) and a dog (B). There is lens capsule rupture, displacement of lens fiber protein, and synechiae in both globes. (C,D) Low magnification and higher magnification of a canine post-traumatic cataract show lens capsular rupture and remodeling.

Traumatic lens subluxation or luxation

This is rarely seen in isolation, as the forces required to disrupt the zonular attachments of domestic animals are generally associated with other signs of severe ocular trauma.

Retinal effects (Figs 5.11, 5.12)

Because of the precise anatomic and functional organization of normal retinal tissue, it is at great risk of damage associated with contusive injury.

- The neuroretinal tissue is 'stretched' across the posterior segment, and it has a semi-liquid consistency that makes it vulnerable to disruption by the shearing forces of a pressure wave propagating within it
  - This type of injury can be associated with 'whiplash' forces, which may result from shaking, as seen in the shaken-baby syndrome in human infants, or from a blow to the head
- If the damage is mild, the retina may not degenerate, and a return to function is possible
- If the damage to the retina is locally severe, the retinal tissue undergoes rapid degeneration. The damage occurs acutely, is non-progressive over the long-term, and it is often segmental
- Within the first 24 h, retinal contusion is associated with apoptosis and physical disruption
  - Separation of the photoreceptor processes from the outer nuclear layer is seen in acute trauma
  - Hemorrhage in the retina or vitreous
- Within 5 days, the severely affected retinal tissue becomes liquefied and phagocytes (gitter cells) predominate
- The end-stage is regional, severe retinal atrophy
  - Retinal detachment and retinal tears are frequently seen
  - A useful clue that trauma was involved as the cause of severe retinal damage is the finding of well-preserved blood vessels, seemingly 'free in space', separated from the atrophic retinal tissue adjacent to them.

Scleral effects, scleral rupture (Figs 5.13, 5.14)

There are over 240 cases of scleral rupture in the COPLOW collection in dogs and cats. Scleral rupture results from a deforming blow to the globe. The blow may or may not directly penetrate the globe but deformation of the globe results in rupture of the sclera at points of weakness. These weak points include the equatorial region adjacent to rectus muscle attachments and, less commonly, the posterior pole.

- Most commonly, scleral rupture is the result of blunt trauma without a penetrating component (Fig. 5.13)
  - In these cases you will find the following features:
    - Segmental uveal fibrosis in the region of the scleral rupture or defect

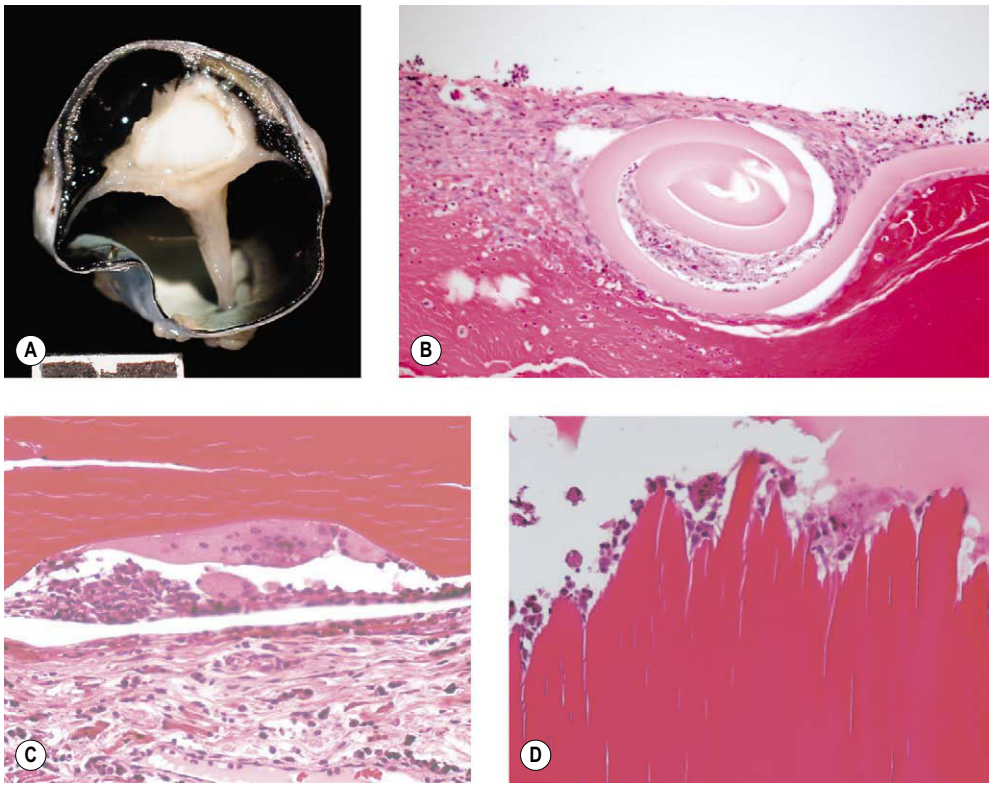


Figure 5.8 Lens capsule rupture. (A) Gross photograph of a canine globe showing a small lens remnant and adhesion of iris, ciliary body, and detached retinal tissue. (B) Photomicrograph of a feline globe after traumatic lens capsule rupture showing coiling of the capsule and cellular proliferation on both sides of the capsular defect. (C,D) Photomicrographs showing macrophage and multinucleate giant cell reaction to exposed lens proteins, which is a reliable indication of lens capsular rupture.

  - A scleral defect, which typically extends from the equator radially towards the posterior pole
  - Episcleral and orbital fibrosis with displaced fragments of pigmented uveal tissue or disorganized neural tissue of retinal origin
  - Episcleral damage involving peripheral nerve tissue, with neuroma formation
- An example of trauma to the globe with both direct penetration and scleral rupture would be a ballistic injury (Fig. 5.14)
  - In these cases, you will find the following features:
    - An entry wound
    - Uveal fibrosis in association with the scleral defect
      - If segmental uveal fibrosis but no scleral defect is found, it can be rewarding to cut deeper into the block in search of a scleral defect
    - A scleral rupture starting at the equator that extends radially toward the posterior pole, but does not involve the optic disc
    - Possibly an exit wound
    - Metallic fragments
      - Polarized light can be very useful to identify tiny, metallic fragments, which otherwise may masquerade as melanin
    - Extensive episcleral and orbital hemorrhage or scarring, depending on chronicity
    - Displaced pigmented uveal tissue and disorganized neural tissue of retinal origin.

Comparative Comments

The retinal effects and scleral effects of blunt trauma are very similar in the human eye to those described for domestic animals.

PENETRATING INJURIES

Corneal penetrating injury (Fig. 5.15)

In the COPLOW collection, it is generally not possible to differentiate penetration of the cornea due to intrinsic, primary corneal disease with perforation (as discussed in greater detail in Ch. 8) from that due to penetrating trauma. Although traumatic penetrating injury to the cornea is undoubtedly important, the unique features and consequences of traumatic corneal penetrating injuries will not be specifically addressed in this chapter, because it is often not possible for the pathologist to establish the sequence of events.

Scleral penetrating injury (Figs 5.16, 5.17)

In the scleral penetrating injury cases recorded in the COPLOW collection, we have seldom been provided with a history of a traumatic event. There are features that suggest a penetrating injury to the sclera, which include the following:

- Episcleral, orbital, and/or subconjunctival fibrosis or fistulating inflammation
  - If the inflammation is more severe in the superior part of the orbit/globe, this suggests injury related to an attack or a falling object
  - If the inflammation is more severe inferiorly, this suggests penetrating injury related to an oral foreign body or a stick from below
    - There are seven cases in the COPLOW collection, as well as cases published in the veterinary literature, with a recent history of dentistry and in some cases, accidental slippage of a dental instrument

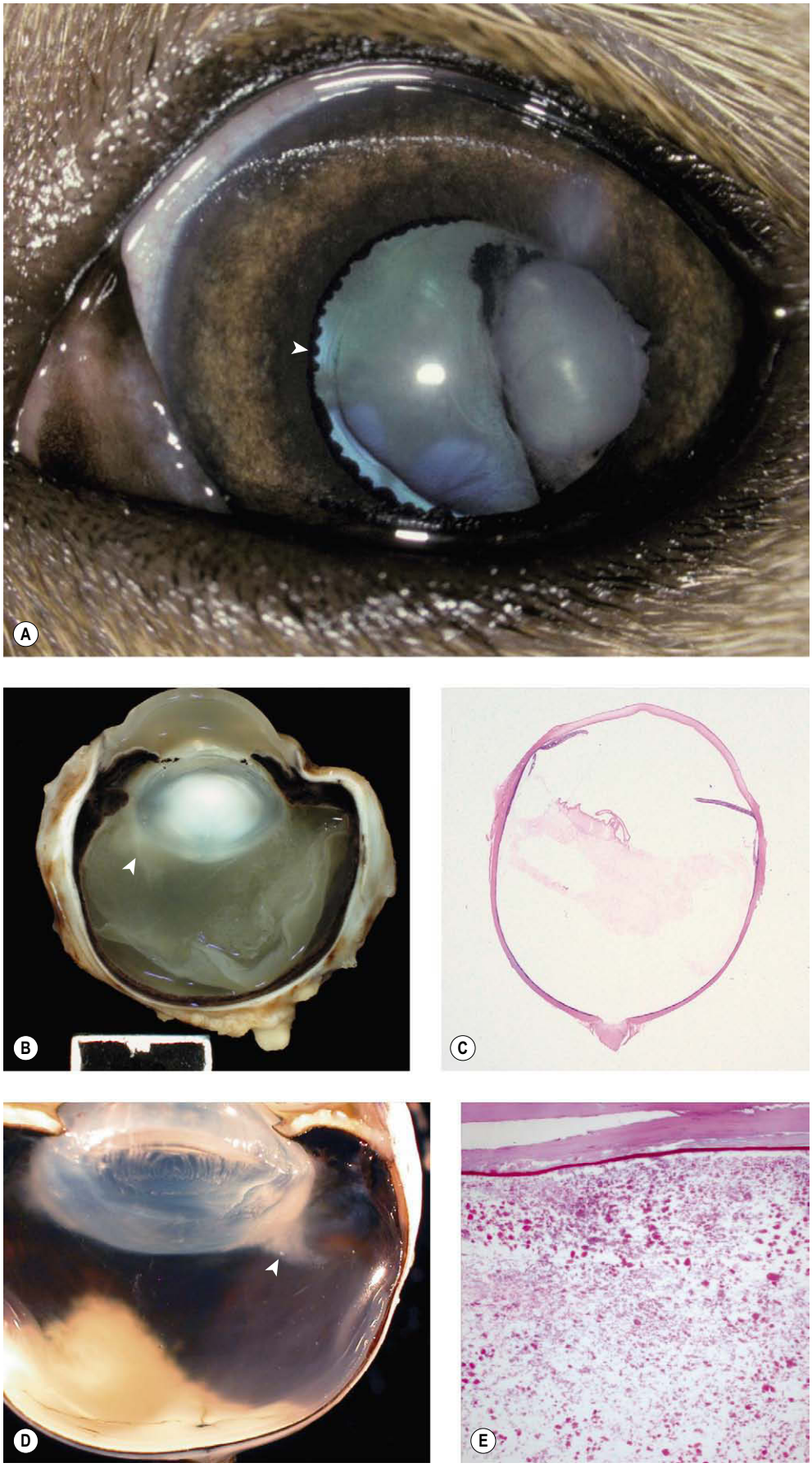


Figure 5.9 Lens-induced uveitis, phacoclastic uveitis. (A) Mixed Breed, 12 weeks old: prior trauma resulted in lens rupture, cataract formation, and uveitis. Pigment is present on the lens and ectropion uvea is indicated by the arrow. (B) Vitreous protein exudation is adjacent to the ruptured lens capsule (arrow) in a traumatized dog globe. (C) Subgross photomicrograph of a canine globe showing a nearly empty lens capsular bag and protein exudates in the vitreous body secondary to the release of denatured lens proteins. (D) Gross photograph of a feline globe showing distinctive protein exudates (arrow) in the vitreous body near the posterior pole of the lens, which is associated with posterior lens capsule rupture and lymphoplasmacytic uveitis. (E) Photomicrograph of the globe in (D) showing the granular hypereosinophilic protein characteristic of posterior lens capsular rupture in feline uveitis.

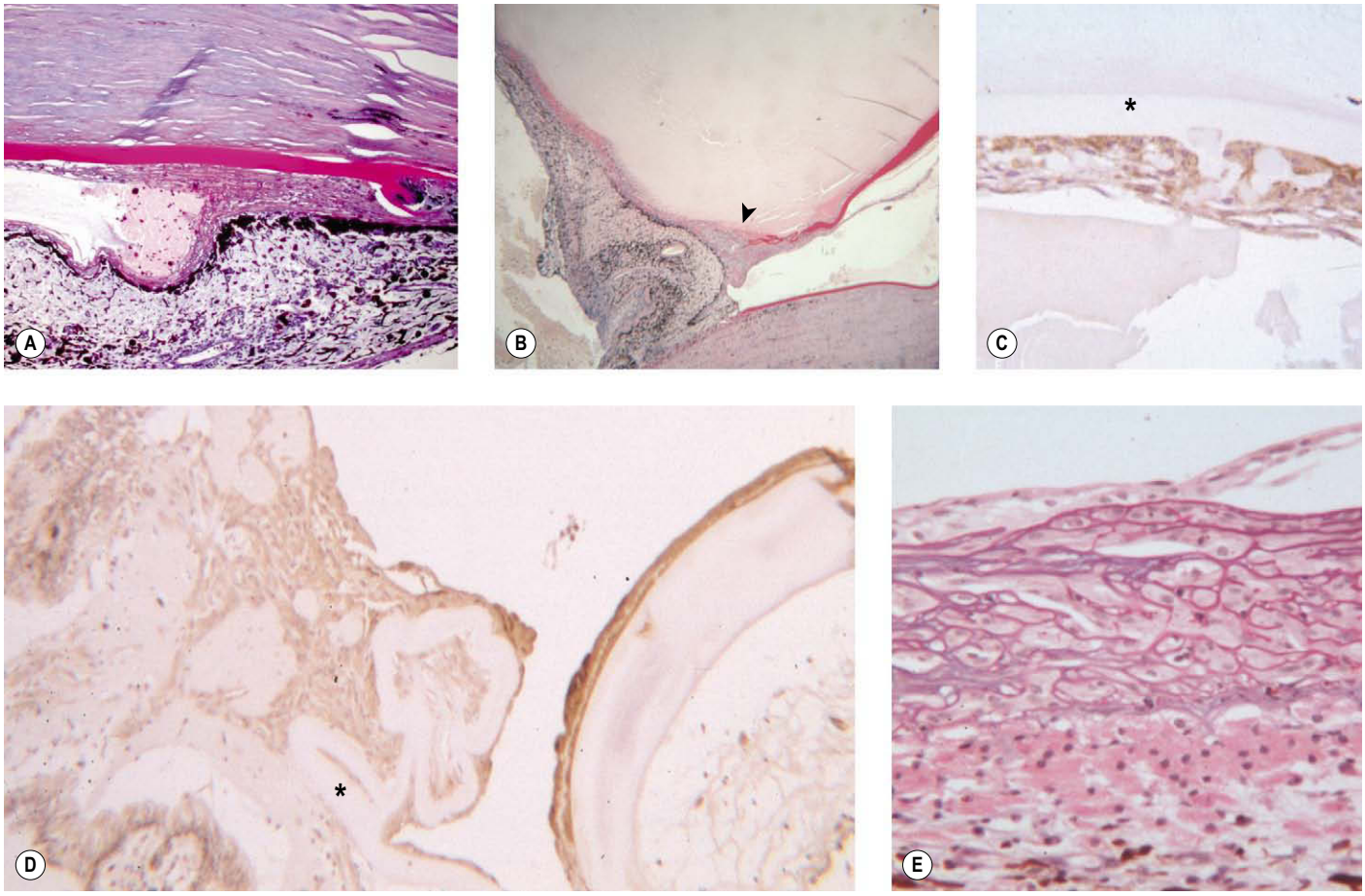


Figure 5.10 Metaplasia and proliferation of released lens epithelial cells. (A) Photomicrograph of a canine globe showing the iridocorneal angle with a spindle cell proliferation and broad anterior synechia secondary to lens epithelial cell proliferation and migration into the anterior chamber. Surrounding each spindle cell is a thick PAS-positive basement membrane, characteristic of lens epithelial cell origin (PAS stain). (B) Low magnification photomicrograph showing lens capsule rupture (arrow), with proliferation and migration of metaplastic lens epithelial cells. The lens is entrapped in the anterior chamber and the proliferating cells are between the lens and the iris (PAS stain). (C,D) Photomicrographs of a traumatized dog globe showing metaplastic lens epithelial cells, labeled with immunohistochemical stain for smooth muscle actin, within the lens capsule (*) (C) and surrounding the wrinkled lens capsule (*) (D). (E) Photomicrograph of a traumatized feline globe showing the tapetum and a membrane on its inner surface composed of metaplastic lens epithelial cells. A distinct PAS-positive basement membrane surrounds individual cells (PAS stain).

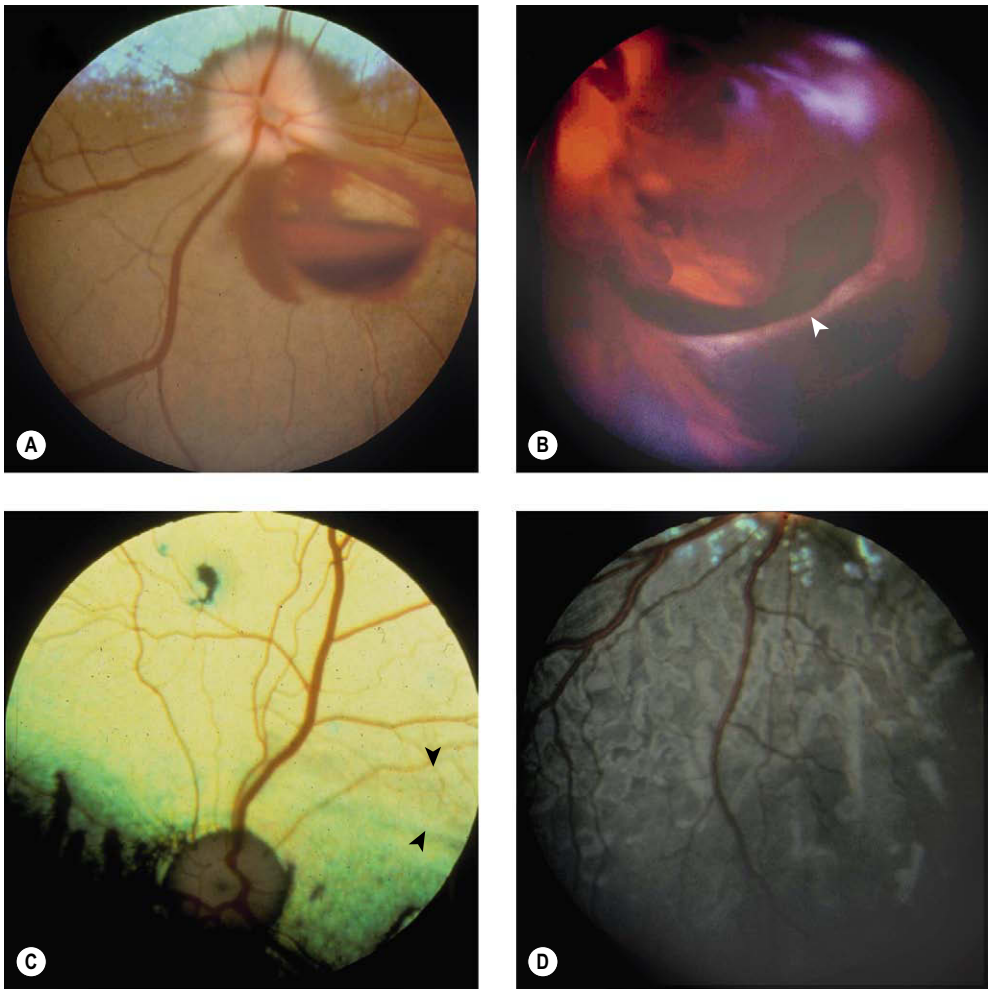


Figure 5.11 Traumatic retinal tear, fundoscopy. (A) Doberman Pinscher, 3.5 years old: blunt trauma caused papilledema and preretinal hemorrhage. (B) Mixed Breed, 3 years old: extensive posterior segment hemorrhage is present after being hit by a car. The arrow points to the edge of a giant retinal tear in the detached retina. (C) Beagle, 1.5 years old: acute blindness was present after being hit by a car. Peripapillary and horizontal linear areas of tapetal hyperreflectivity are present (black arrows). Abnormal tapetal pigmentation is also present. (D) Non-tapetal fundus of the globe in (C). Linear areas of depigmentation and pigment migration in the outer layer of the retina are present.

- A full-thickness scleral defect
  - This finding is good evidence of a penetrating injury but, unfortunately, is seldom found in the standard plane of section
- Some evidence of direct damage within the globe, that includes at least one of the following (Fig. 5.17):
  - Lens capsule rupture
  - Fistulous inflammatory tracts that extend through the uvea or retina
  - Bacterial sepsis
  - Identification of a fragment of foreign material in the section
    - By far the most common foreign body found in tissues in the COPLOW collection is a plant fragment (32 cases). However, hair, mineral (three cases), bone, feather, metal, and plastic have also been found. Porcupine quills are not uncommon as causes of penetrating or perforating ocular injury in certain geographic locations.

Suppurative endophthalmitis (Fig. 5.18)

- Suppurative endophthalmitis is the most common consequence identified in eyes removed after a penetrating injury
  - Among dogs, the brachycephalic breeds (also prone to keratitis) are most likely to have suppurative endophthalmitis
    - The Shih Tzu is the most commonly represented canine breed, accounting for 121 of the 954 cases in the COPLOW collection with this diagnosis
  - Larger hunting breeds, perhaps due to their propensity for running through brush, are also prone to endophthalmitis related to perforating/penetrating injuries
- Common morphologic features of suppurative endophthalmitis associated with penetrating injury include (Fig. 5.18):
  - A similarity in the degree of suppurative exudates throughout all of the compartments of the globe
  - Lens capsule rupture
  - Liquefactive necrosis of the retina
  - Focal or multifocal, very localized neovascular extensions from the choroid into the subretinal space
    - At COPLOW, these neovascular extensions are often referred to as 'volcanoes' because of their eruptive appearance
  - A very early change, seen in acute cases, is the appearance of suppurative infiltrate within the choriocapillaris, before other exudates are apparent.

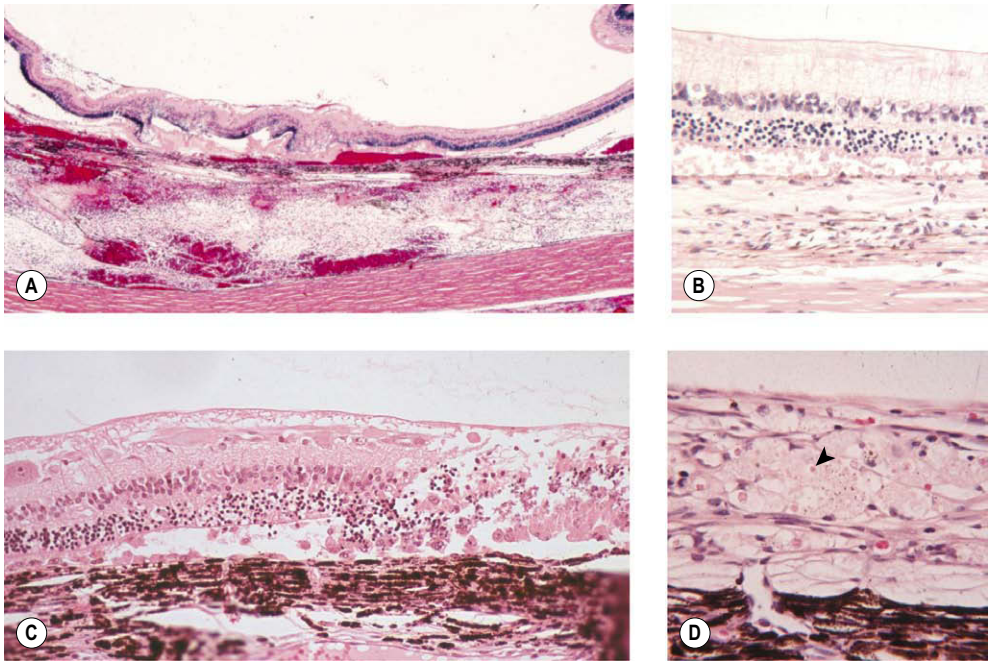


Figure 5.12 Retinal trauma, microscopic. (A) Photomicrograph showing the effects of recent trauma on the retina from a canine globe penetrated by a pellet 5 h before enucleation. There is hemorrhage and a segmental loss of structural integrity. (B) Photomicrograph of the retina from a young horse necropsied 24 h after a head trauma showing segmental apoptosis of photoreceptors and disruption of inner and outer segments. (C) Photomicrograph of the retina from a dog necropsied 5 days after head trauma showing segmental retinal disruption, necrosis and phagocyte accumulation. (D) Photomicrograph showing complete retinal atrophy with remaining macrophage cells (gitter cells) (arrow) 10 days after blunt trauma.

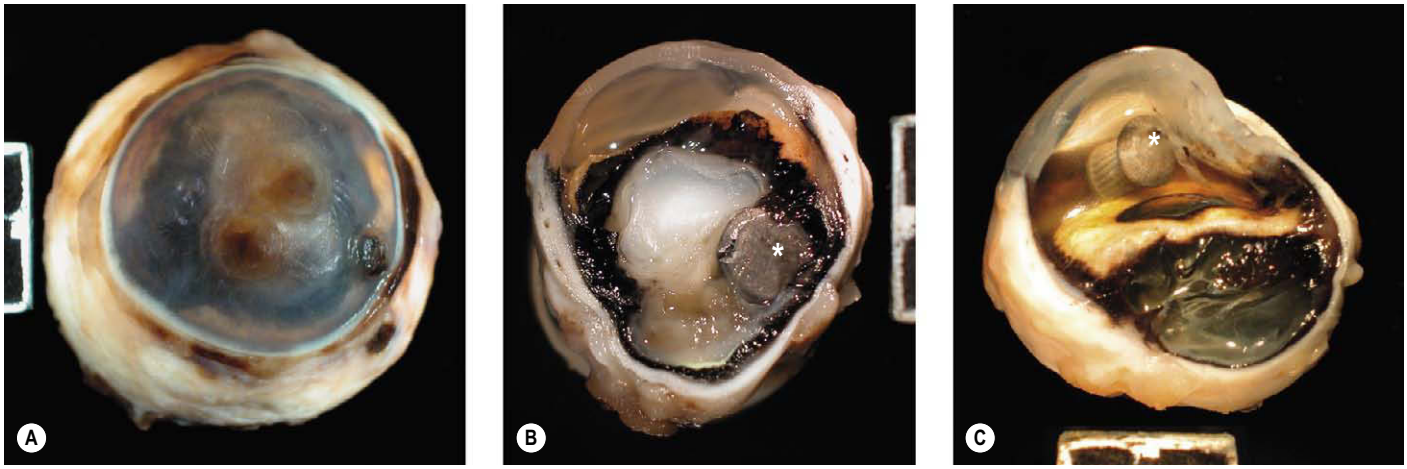


Figure 5.13 Ballistic foreign bodies in the globe. (A) Anterior view of a canine globe removed shortly after penetrating trauma from a shotgun injury. (B,C) A dog globe (B) and a cat globe (C) show disorganization of ocular tissues associated with bullet fragments (*) visible within the globe.

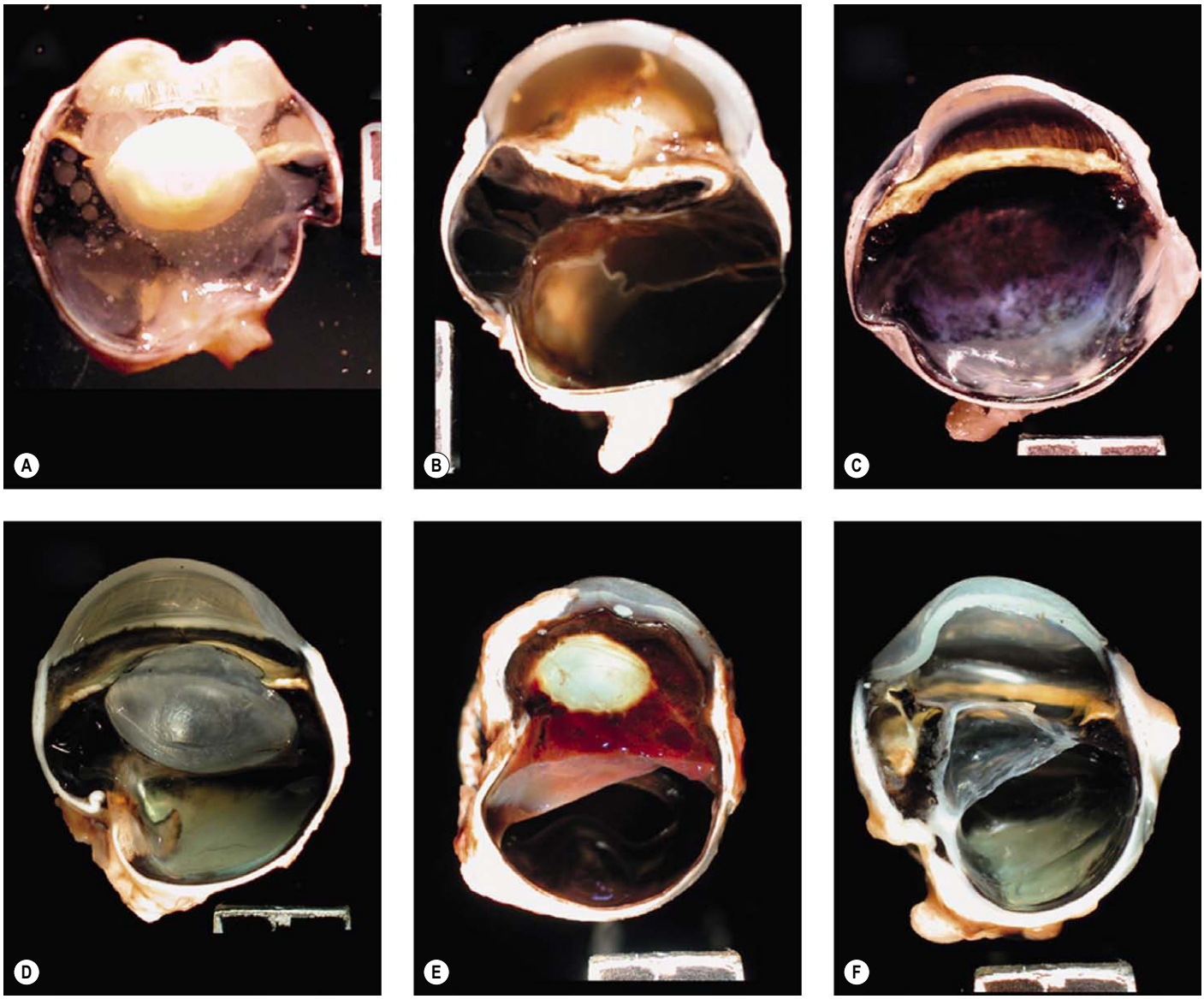


Figure 5.14 Scleral rupture, blunt trauma. (A–F) A montage showing six dog and cat globes with scleral rupture associated with blunt trauma. Scleral rupture in blunt trauma starts at the equator, where the sclera is thinnest, and extends towards the posterior pole.

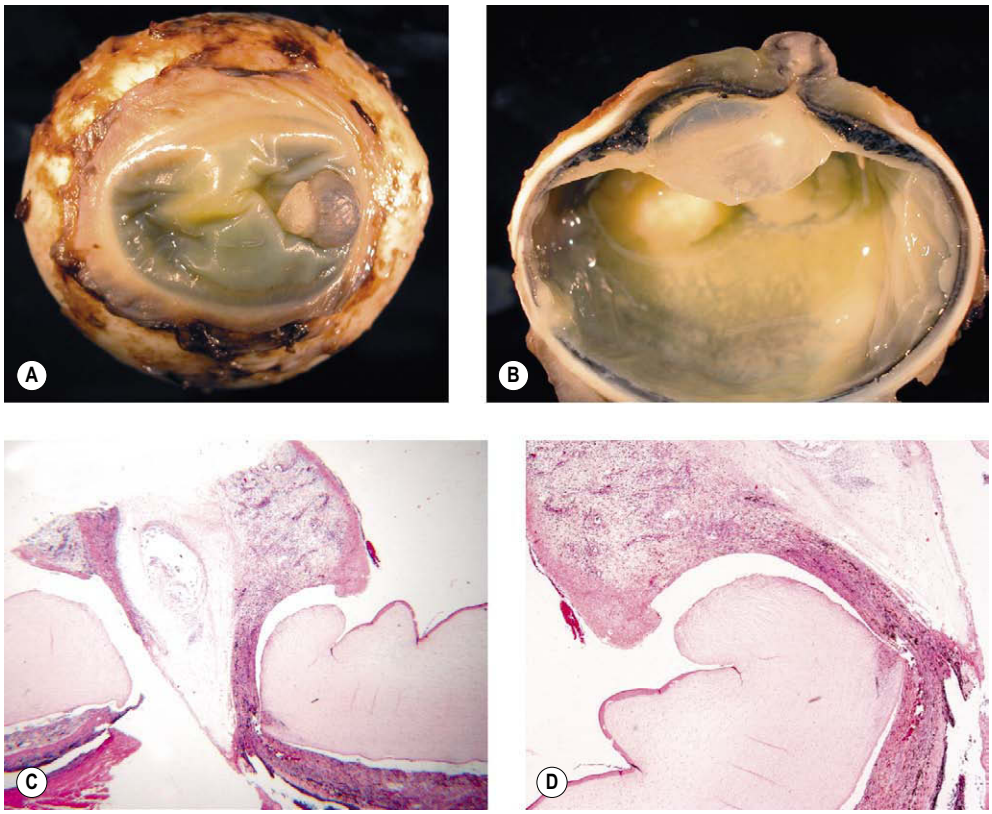


Figure 5.15 Traumatic corneal perforation. (A,B) Gross photographs of a canine globe with traumatic corneal perforation and iris prolapse. (C,D) Low magnification photomicrographs of the same globe showing iris tissue prolapsed through the cornea and entrapped, leading to swelling, edema and vascular proliferation.

Septic implantation syndrome ('cat scratch' injuries) (Figs 5.19, 5.20) (see also Ch. 10)

- This is a canine and feline syndrome of endophthalmitis, often resulting from cat scratch injury, that can be defined by a specific set of morphologic criteria:
  - There are 75 canine and 20 feline eyes in the COPLOW collection with endophthalmitis and features of 'septic implantation syndrome'
  - All ages are affected but there is a bias towards younger animals
- A definitive history of known cat scratch injury is seldom provided. However, when the inciting cause *is* known, it is often related to an incident involving a cat scratch
- A feature of this syndrome is a period of latency, during which the globe is relatively quiet, between the inciting injury and the onset of endophthalmitis that leads to enucleation
  - A latency period of several months is typical, but latencies as long as 2 years have been observed among the cases in the COPLOW collection
- This syndrome is characterized by the following morphological features:
  - Suppurative and histiocytic inflammation which intimately surrounds the lens
  - Broad posterior synechiae, with spindle cells and collagen that are consistent with temporal chronicity
  - Lens capsule rupture with suppurative inflammation extending into the lens substance
  - About 60% of cases have identifiable bacterial colonies within the lens substance but away from the inflammatory cell infiltrate
    - In affected canine eyes, bacteria are usually Gram-positive cocci
    - In feline cases there is more likely to be a mixed population of bacteria.

Comparative Comments

The sequelae of perforating injuries in the human eye are similar to those discussed in the COPLOW collection.

CHEMICAL INJURY (Fig. 5.21)

In contrast to the situation in human ocular pathology services, submissions to COPLOW from cases affected by known chemical injury are extremely rare.

Acid burn

Acid exposure to tissue causes an instantaneous coagulation of the most superficial tissues, with precipitation of proteins, but the effect does not extend deeply.

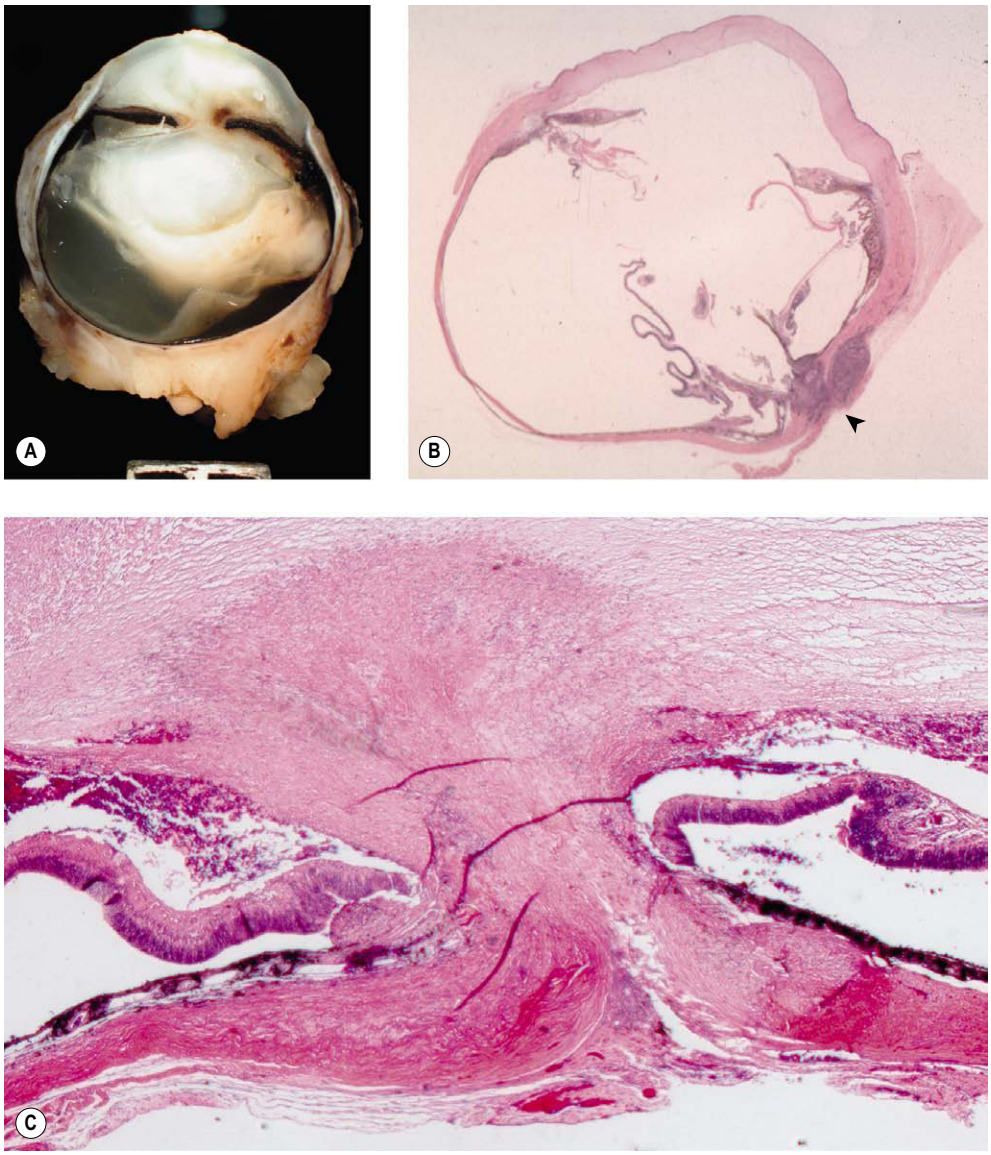


Figure 5.16 Traumatic penetrating injury. (A) Gross photograph of a canine globe with endophthalmitis due to a penetrating injury. (B) Subgross photomicrograph of a canine globe penetrated by a migrating porcupine quill. The arrow indicates the point of scleral penetration. (C) Photomicrograph showing the scleral penetration point from a slipped dental instrument.

- Acute: coagulation necrosis of superficial epithelial and stromal tissues
- Chronic: granulation tissue response.

Alkali burn

Alkali exposure causes extensive damage due to its ability to penetrate deeply into ocular tissue.

- Acute: There is swelling and loss of the corneal epithelium and coagulation of conjunctival blood vessels. Tissue swelling and vascular damage extend deep into the tissue, with intraocular extension of these effects
- Chronic: tissue atrophy, collagenolytic lysis, and granulation tissue. Keratomalacia is associated with the release of collagenases from corneal epithelial and stromal cells, and from neutrophils.

Snake bite (Fig. 5.22)

There are three cases in the COPLOW collection of venomous snake bites directly to the globe.

- The damage is dominated by tissue lysis, presumed to be related to lytic factors in the venom
- Retinal and optic nerve tissue are notably destroyed, and seemingly liquified.

PROPTOSIS AND OPTIC NERVE TRAUMA (Figs 5.23, 5.24)

There are 82 cases in the collection with a history of proptosis (anterior prolapse of the globe, which becomes entrapped by the eyelid margins behind the globe equator).

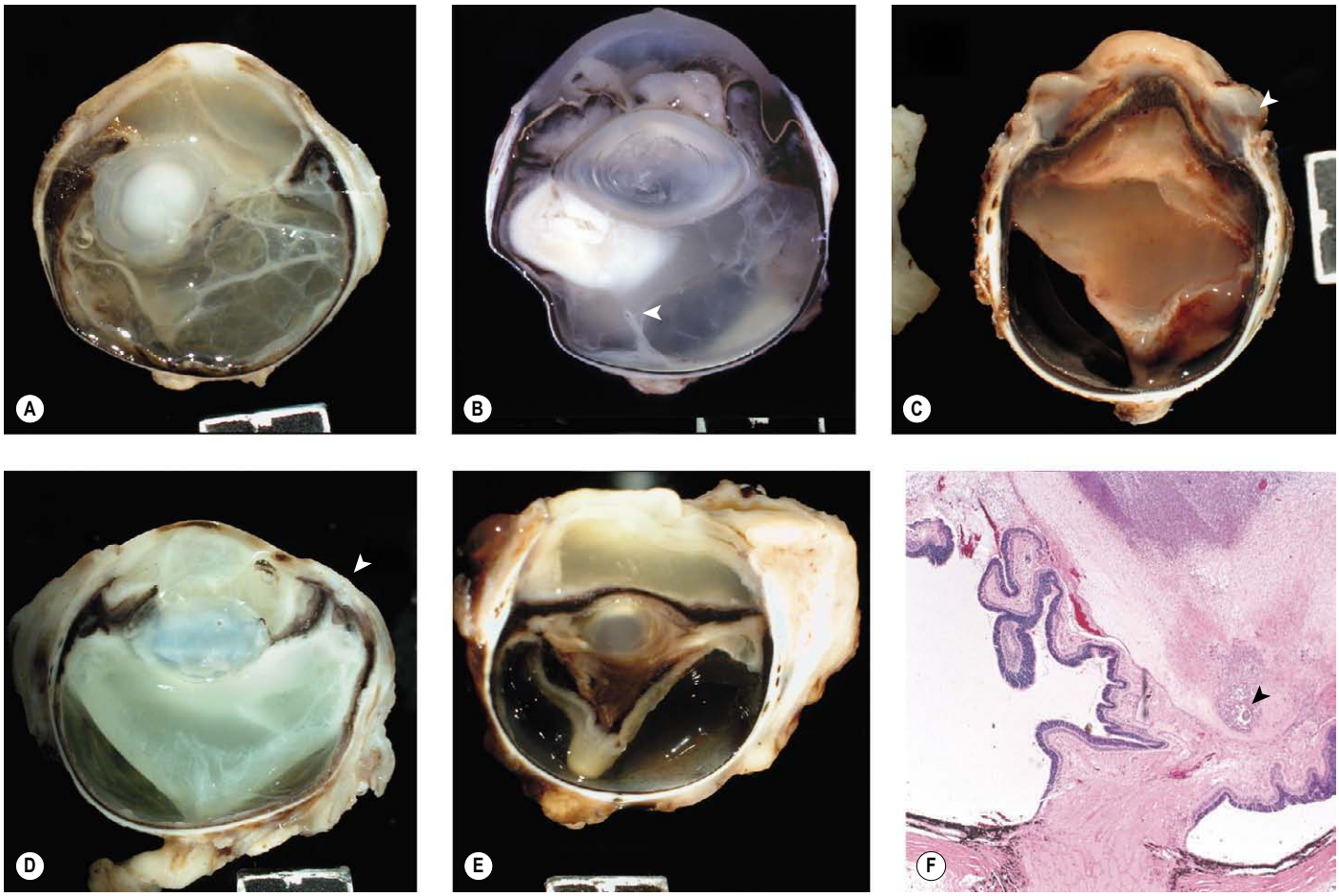


Figure 5.17 Endophthalmitis with a foreign body. (A–E) A montage of gross photographs of canine and feline globes with scleral penetrating injuries. White arrows in images (B), (C) and (D) indicate the points of penetration or tracks within the globe. (E) Low magnification photomicrograph showing a plant foreign body (black arrow) imbedded in the globe near the optic nerve.

- Of these 82, 80 are dogs and only two are cats. Brachycephalic breeds, young dogs, and small terrier breeds are over-represented
- The time between proptosis and subsequent enucleation ranges from hours to months
- The morphologic features in enucleated canine globes with a history of proptosis include:
  - Global optic nerve necrosis
    - Most globes removed following proptosis have immediate total necrosis of the optic nerve tissue
    - If removed within 4 days of proptosis, degeneration of the neuropil and apoptotic nuclear profiles will be observed within the optic nerve
    - If removed 5–10 days after proptosis, optic nerve tissue malacia, dominated by macrophage cells (gitter cells) will be observed
    - If removed 2 weeks or more after proptosis, profound atrophy and fibrosis of the optic nerve will be observed
  - Retinal effects
    - The effects of retinal contusion (as described previously) may be observed
      - Detachment and/or retinal tear
      - Segmental malacia followed by atrophy
    - A loss of retinal ganglion cells secondary to the optic nerve trauma may be observed and, when seen, the loss of ganglion cells occurs within days of the traumatic episode
  - Corneal effects
    - In proptosed eyes, acute and profound corneal necrosis occurs, because of desiccation, loss of innervation and/or loss of blood supply to the anterior segment. There can be a full-thickness devitalization of the corneal stroma. This is purportedly more likely to occur if avulsion of more than two extraocular muscles is recognized
    - Loss of corneal sensation or reduced ability to blink may also contribute to chronic keratitis, following surgical replacement of a proptosed globe
  - In rare cases, total infarction of the globe may occur after proptosis resulting in global necrosis of ocular tissues
  - Orbital effects
    - Muscle damage, orbital hemorrhage, and other effects of soft tissue trauma can lead to inflammation or scar tissue in the episclera and orbital tissue.

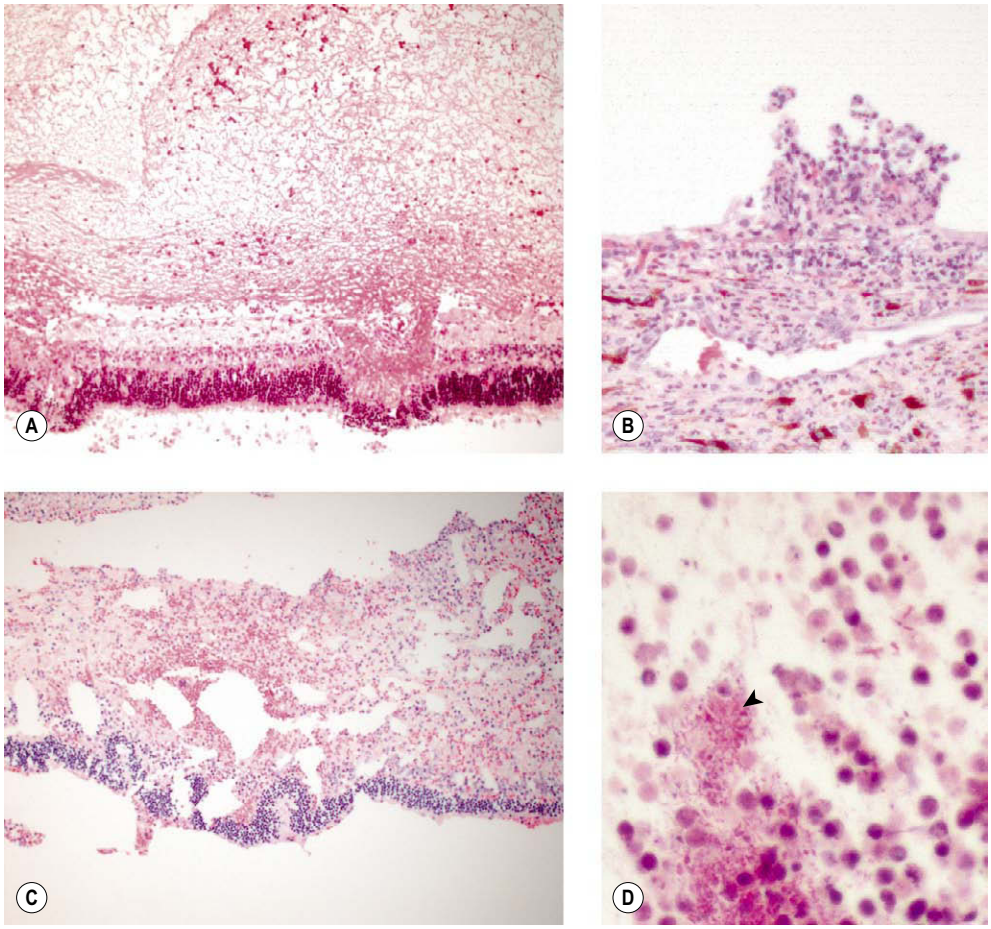


Figure 5.18 Suppurative endophthalmitis, microscopic. (A) Photomicrograph showing liquefactive necrosis of retinal tissue in suppurative endophthalmitis. (B) Photomicrograph showing a focal proliferative lesion in the choriocapillaris from a dog with suppurative endophthalmitis. (C) Photomicrograph showing retinal necrosis and neutrophilic infiltration. (D) High magnification photomicrograph showing bacteria in the vitreous body (arrow).

END-STAGE DISEASE (ATROPHY OF THE GLOBE AND PHTHISIS BULBI) (Fig. 5.25)

Many of the consequences of trauma to the globe result in a proliferative response which extends into the anterior and posterior chambers and the vitreous body, and this may be accompanied by tissue atrophy.

- Cell types that participate in the proliferative response include:
  - Corneal endothelium and deep corneal stromal cells
  - Ciliary body epithelial cells
  - Vascular endothelial cells and spindle cells from the anterior iris, posterior iris, ciliary body, or choroid
  - Vascular endothelial cells or spindle cells associated with the optic nerve head
- It is noteworthy that the proliferative response in the globe seldom causes pronounced distortion or fibrosis of the uvea itself.
  - Tissue proliferation within ocular compartments and chambers can undergo contracture, a feature of granulation tissue throughout the body
- Contracture of the proliferating tissues of the globe, in combination with a failure to produce aqueous humor leads to atrophy and shrinkage of the globe. Often, this shrinkage of the globe is accompanied by disorganization and distortion of ocular tissues, and is termed 'phthisis bulbi'
- Other effects often seen are mineralization and osseous metaplasia.

Comparative Comments

Phthisis bulbi in the human consists of shrinkage, atrophy, and degeneration similar to that seen in animal eyes.

Feline post-traumatic ocular sarcoma (FPTOS) (Figs 5.26–5.37)

This malignant neoplasm is the third most common intraocular tumor in cats in the COPLOW collection, with 234 diagnosed. There are three morphological variants of FPTOS, all of which tend to line the inner aspect of the globe:

1. Spindle cell variant (lens epithelial cell-derived): 70% (Fig. 5.26)
2. Round-cell variant (B-cell lymphoma): 24% (Fig. 5.27)
3. Osteosarcoma/chondrosarcoma: 6% (Fig. 5.28).

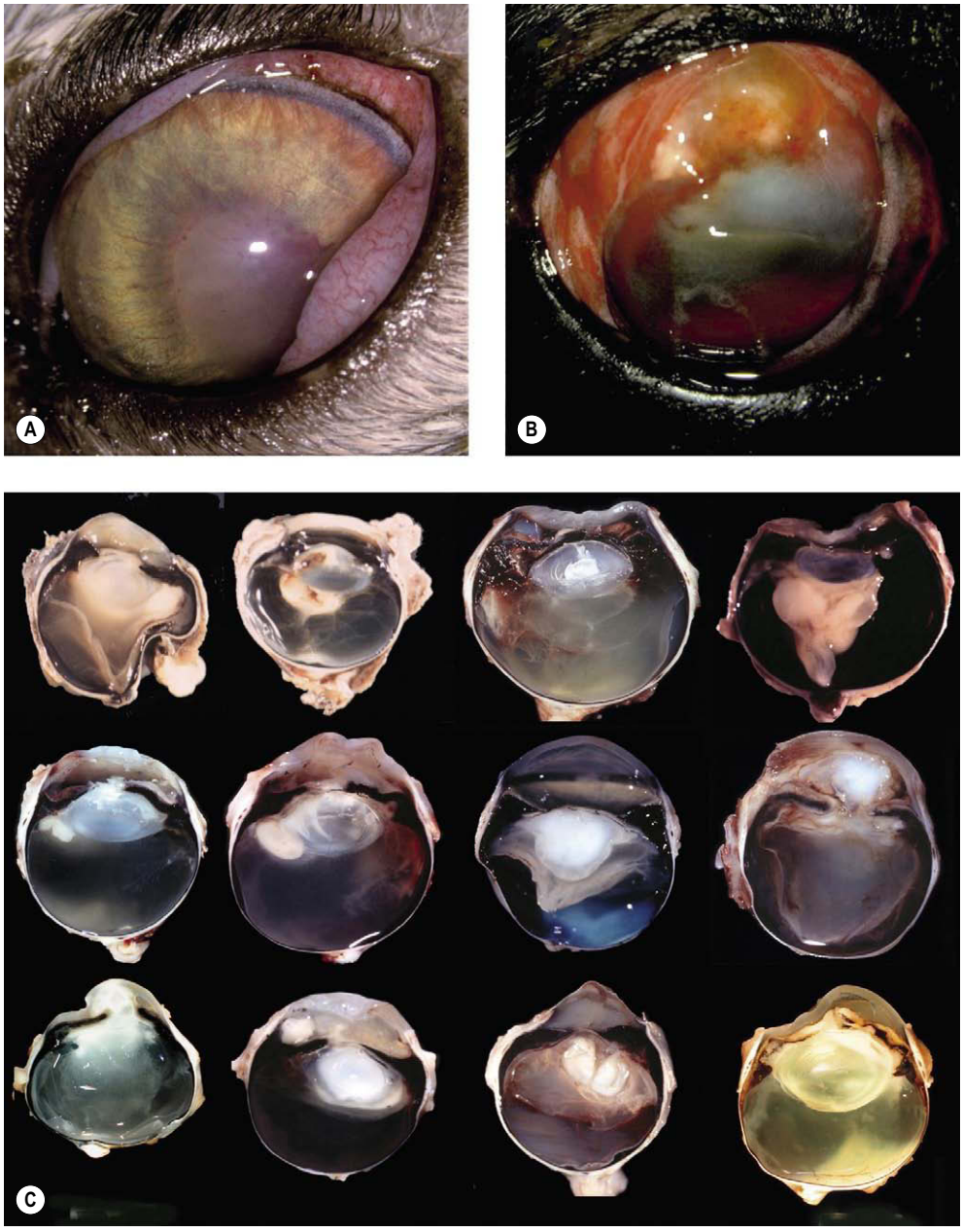


Figure 5.19 Septic implantation syndrome. (A) Persian, 5 years old: the lens was ruptured and posterior synechiae developed. Gram-positive cocci were identified. (B) Boxer, 4 years old: a penetrating injury at the superior limbus was the cause of the severe ocular inflammation. Gram-positive cocci were identified. (C) Each of 12 canine and feline globes with septic implantation syndrome showing endophthalmitis centered on a ruptured lens.

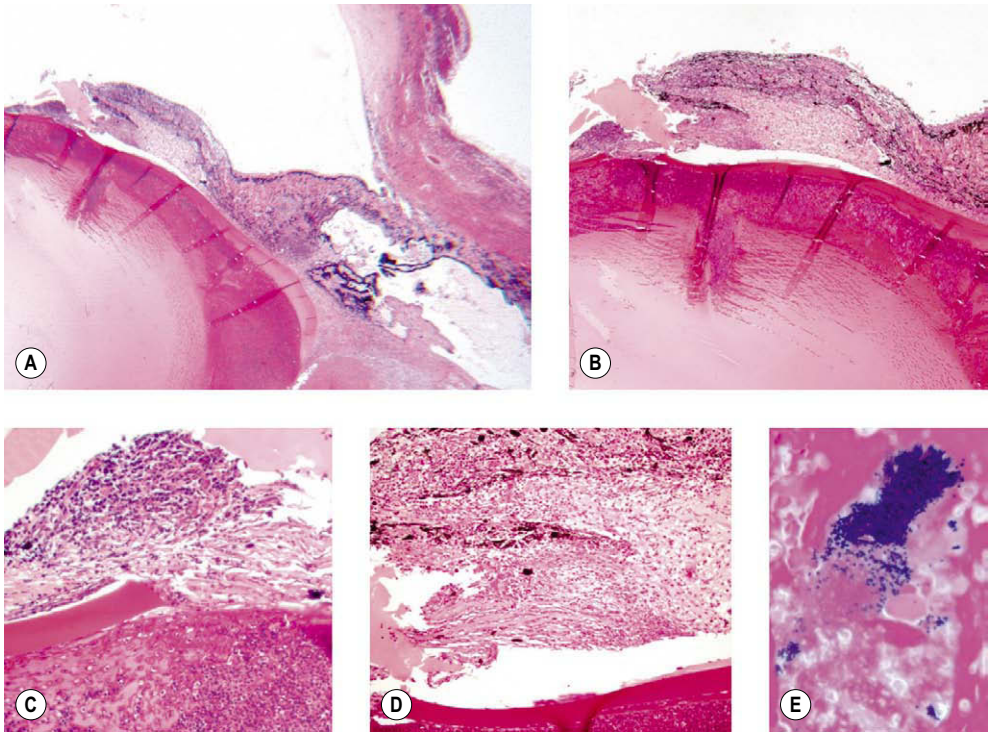


Figure 5.20 Septic implantation syndrome, microscopic. (A,B) Photomicrographs of the same globe show lens capsule rupture and deep implantation of suppurative exudates into the lens. (C,D) Photomicrographs show the ruptured lens and spindle cell proliferation on the anterior surface of the lens. (E) Gram-positive cocci are embedded in a cataractous lens away from the suppurative exudates.

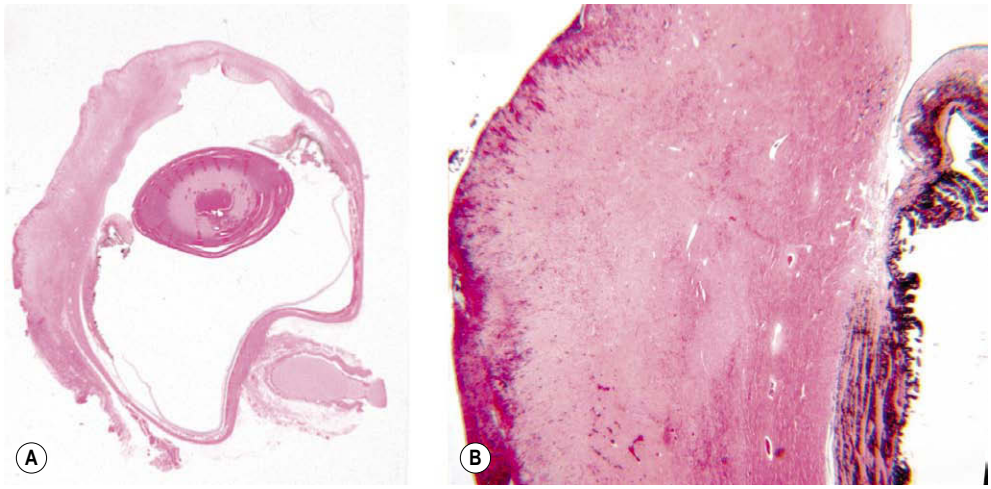


Figure 5.21 Acid burn. (A,B) Subgross and low magnification photomicrographs of a canine globe show extensive tissue fibrosis following an acid burn on the cornea and conjunctiva.

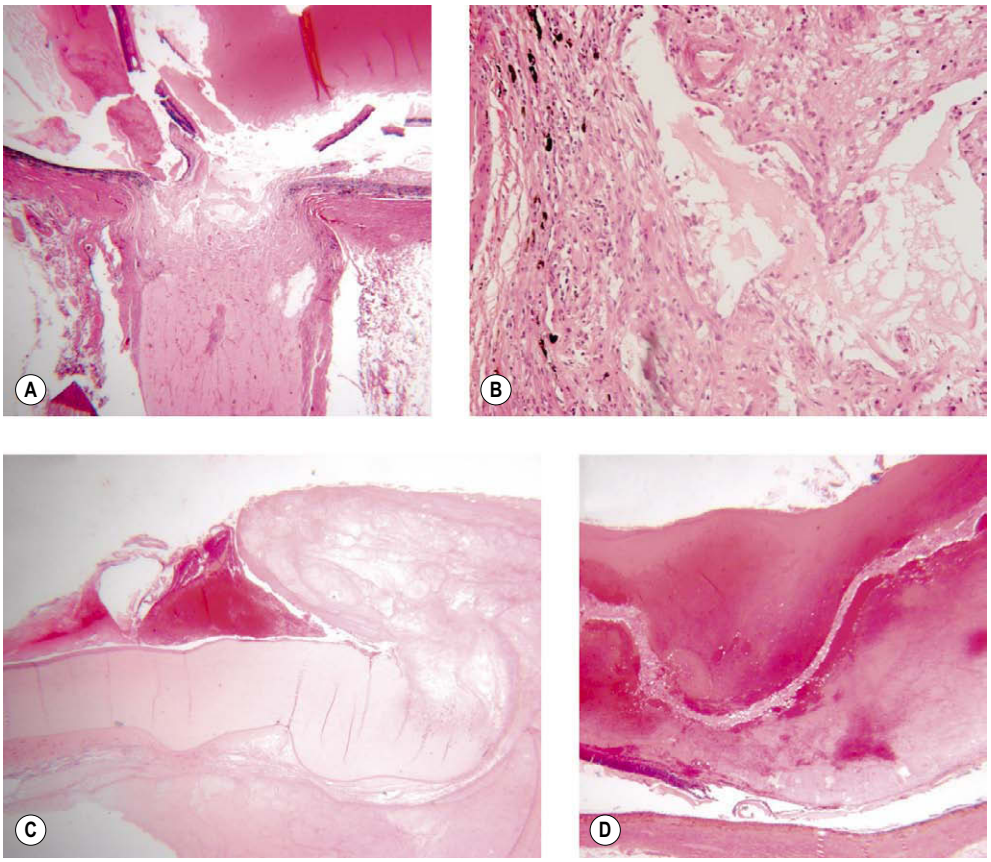


Figure 5.22 Snake bite. (A–D) Photomicrographs of a canine globe show extensive necrotic changes in ocular tissues after a rattlesnake bite directly to the globe. (A) and (B) show the optic nerve, (C) shows corneal necrosis and rupture and (D) shows extensive hemorrhage.

Spindle cell variant FPTOS (Figs 5.26 and 5.29–5.33)

Of the FPTOS cases in the COPLOW collection, 70% are spindle cell variant.

- Epizootiologic features of spindle cell variant FPTOS:
  - This neoplasm typically occurs in cats with a prior history of severe ocular disease
  - The tumors typically demonstrate a long latency period after the initiating injury, but can be recognized from 2 months (rare) to more than 10 years (common) after a traumatic injury. The average time between a traumatic event and enucleation for FPTOS is 7 years
  - Almost all cases have histologically identified lens capsule rupture
  - Only about 20% of cases submitted to COPLOW have a history that documents a known traumatic incident, but many of the cats reportedly had abnormal eyes when acquired as kittens or as adopted adults
- Morphologic features of spindle cell variant FPTOS (Fig. 5.29):
  - Distribution in the globe
    - There is generally extensive involvement of the tissues of the globe, with infiltration of the iris, ciliary body, peripheral cornea, and the atrophic remnants of retinal tissue
    - Tumors tend to line the inner aspect of the choroid internal to the choriocapillaris
    - Tumors may infiltrate the sclera, peripheral nerve tissue and the optic nerve
    - Tumors that are sampled at a relatively early stage in the neoplastic process occur adjacent to the wrinkled lens capsule
- Cellular features of spindle cell variant FPTOS (Fig. 5.30):
  - These are pleomorphic, mesenchymal neoplasms, with cellular features that can range from fusiform spindle cells to polygonal cells, with marked anaplastic features
  - About 10% of tumors have prominent multinucleate giant cells with large numbers of nuclei. The phenotype of these giant cells differs from that of the main population of neoplastic cells, in that:
    - Their nuclear profile is not as anaplastic
    - They do not demonstrate positive intranuclear p53 antigen staining even when all the surrounding cells do (Fig. 5.31)
    - Many tumors have at least some localized areas where PAS-positive staining, suggestive of thick basement membranes, surrounds individual tumor cells, or segments of individual tumor cells
- Immunohistochemical features of spindle cell FPTOS (Fig. 5.32)
  - Neoplastic cells may be positively immuno-labeled with the following immuno-histochemical markers:
    - Vimentin, in almost 100% of affected eyes
    - Smooth muscle actin, in about 20% of affected eyes
    - Broad spectrum cytokeratin, in about 15% of affected eyes
    - Alpha A Crystallin, in about 33% of affected eyes

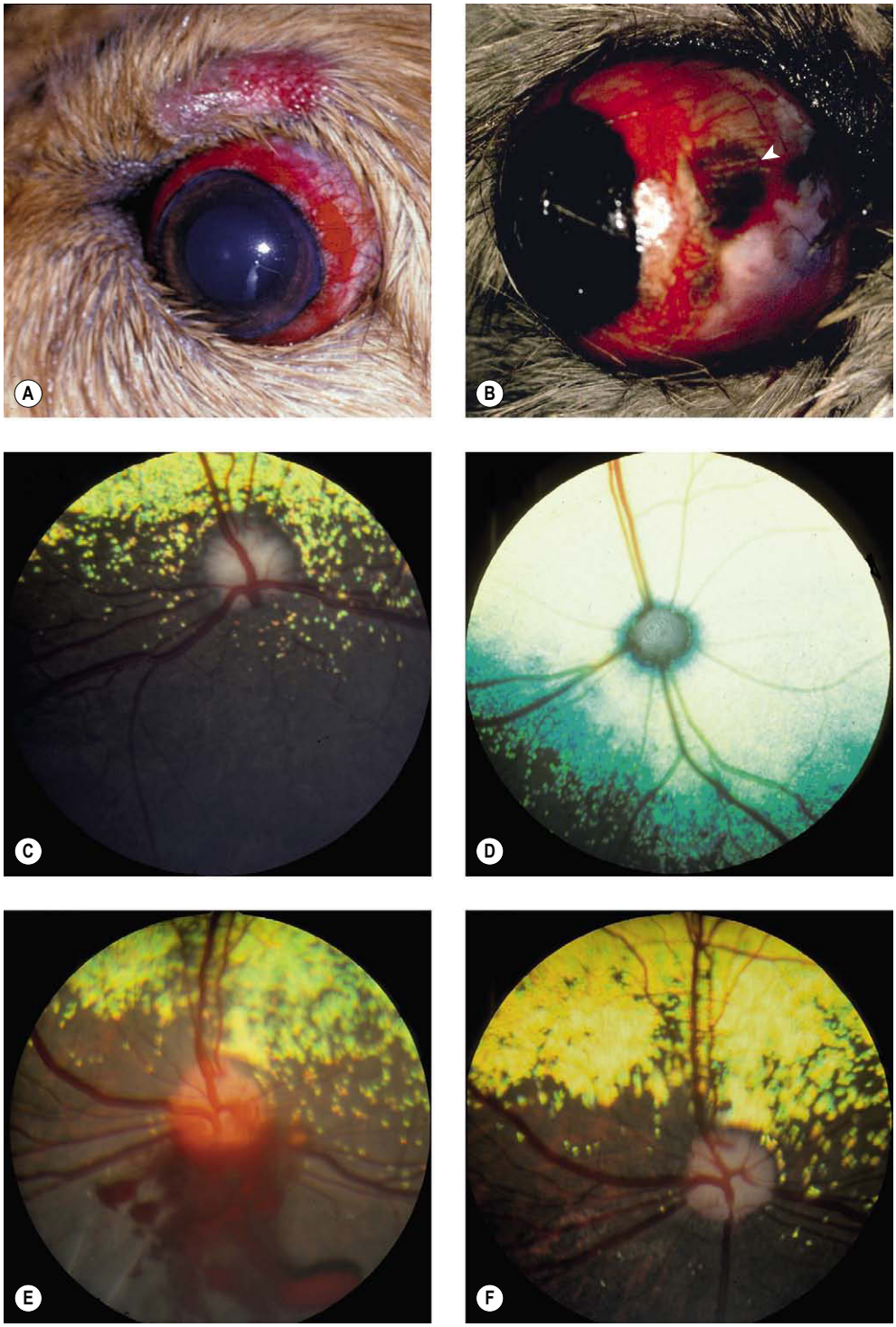


Figure 5.23 Proptosis, clinical. (A) Mixed Breed, 2 years old: the lids are trapped behind the globe. The pupil is dilated. (B) Shih Tzu, 2 years old: following the proptosis of the right globe, this dog was blind in both eyes. The arrow is at the insertion of the avulsed medial rectus muscle. (C) Lhasa Apso, 5 years old: previous proptosis led to a pale, slightly depressed optic disc, characteristic of atrophy, in this blind eye. (D) DSH, 3 years old: the optic disc is extremely pale in this blind eye, 1 year after proptosis. (E) Peke-a-poo, 1 year old: Retinal edema, preretinal hemorrhage and optic nerve head swelling are visible 1 week post-trauma. (F) Same eye as in (E), 7 weeks later. Hemorrhage and swelling have resolved, but the disc is pale and slightly depressed in this blind eye.

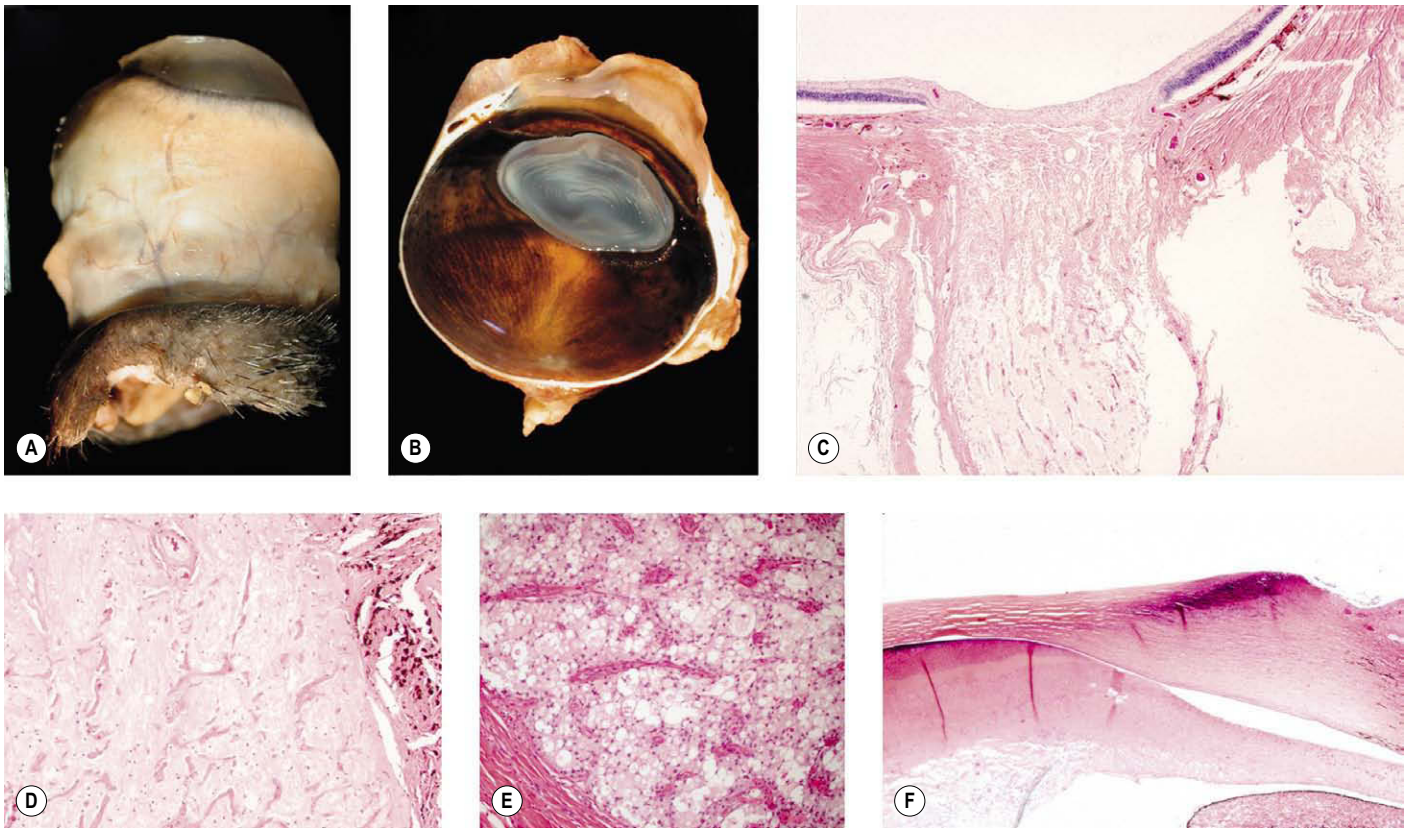


Figure 5.24 Proptosis, pathology. (A) Gross photograph of a canine globe removed after proptosis showing exposure of the episcleral tissues deep in the orbit and corneal desiccation. (B) Gross photograph of a globe removed 3 days after proptosis showing diffuse necrosis of the optic nerve. (C) Photomicrograph of optic nerve necrosis from the same globe as (B). (D) Photomicrograph of the optic nerve from a proptosed canine globe removed immediately after trauma. (E) Photomicrograph of the optic nerve from a globe removed 6 days after proptosis showing malacia of the tissue and gitter cell infiltration. (F) Low magnification photomicrograph showing corneal desiccation in a proptosed globe.

  - The PAS-positive extra-cellular matrix labels positively for collagen type IV, which is characteristic of basement membrane/basal lamina
- Features that support a lens epithelial origin for FPTOS:
  - Lens capsule rupture is almost universally present in affected cats
  - In large tumors other than FPTOS, lens capsule rupture is only occasionally observed
  - Early tumors develop around the lens (Fig. 5.33)
  - The presence of lens capsule-like basement membrane surrounding the neoplastic cells in at least some areas of many of these tumors.
  - Positive labeling of alpha A crystallin in some tumors
- Prognosis
  - Spindle cell variant FPTOS can be highly locally invasive, with extension into optic nerve, peripheral nerve and through the sclera into the orbital soft tissues
  - Local orbital recurrence is common following enucleation.
  - Extension along the optic nerve or peripheral nerve to the brain is common.
  - Distant metastasis may occur, but its incidence is unknown
  - One should carefully evaluate the specimen, attempting to gather evidence of prognostic value:
    - Evidence of extension beyond the sclera indicates a poor prognosis. The prognosis appears to be better if the tumor is confined within the globe
    - A careful evaluation of the optic nerve should be made, including examination of the portion of the nerve farthest away form the globe. Evidence of optic nerve involvement carries a poor prognosis.

Round-cell variant FPTOS (Figs 5.27 and 5.34)

There are 54 cases of round-cell variant FPTOS in the COLPOW collection, representing 24% of the total FPTOS cases. The round-cell variant is also associated with longstanding ocular disease, and the vast majority have lens capsule damage. However, there are a few cases in the collection where the lens is either intact or had been previously removed

- Morphologic features of round-cell variant FPTOS (Fig. 5.34):
  - Distribution in the globe
    - The round-cell variant also fills the globe, but the tumor is much more likely to be effacing than the spindle cell variant, and is less likely to line the inner aspect of the globe
    - The round-cell variant may extend beyond the sclera, but does not infiltrate deeply into the optic nerve or peripheral nerves
- Cellular features of round-cell variant FPTOS:
  - Typically there is extensive tumor necrosis, with viable neoplastic cells surviving around blood vessels

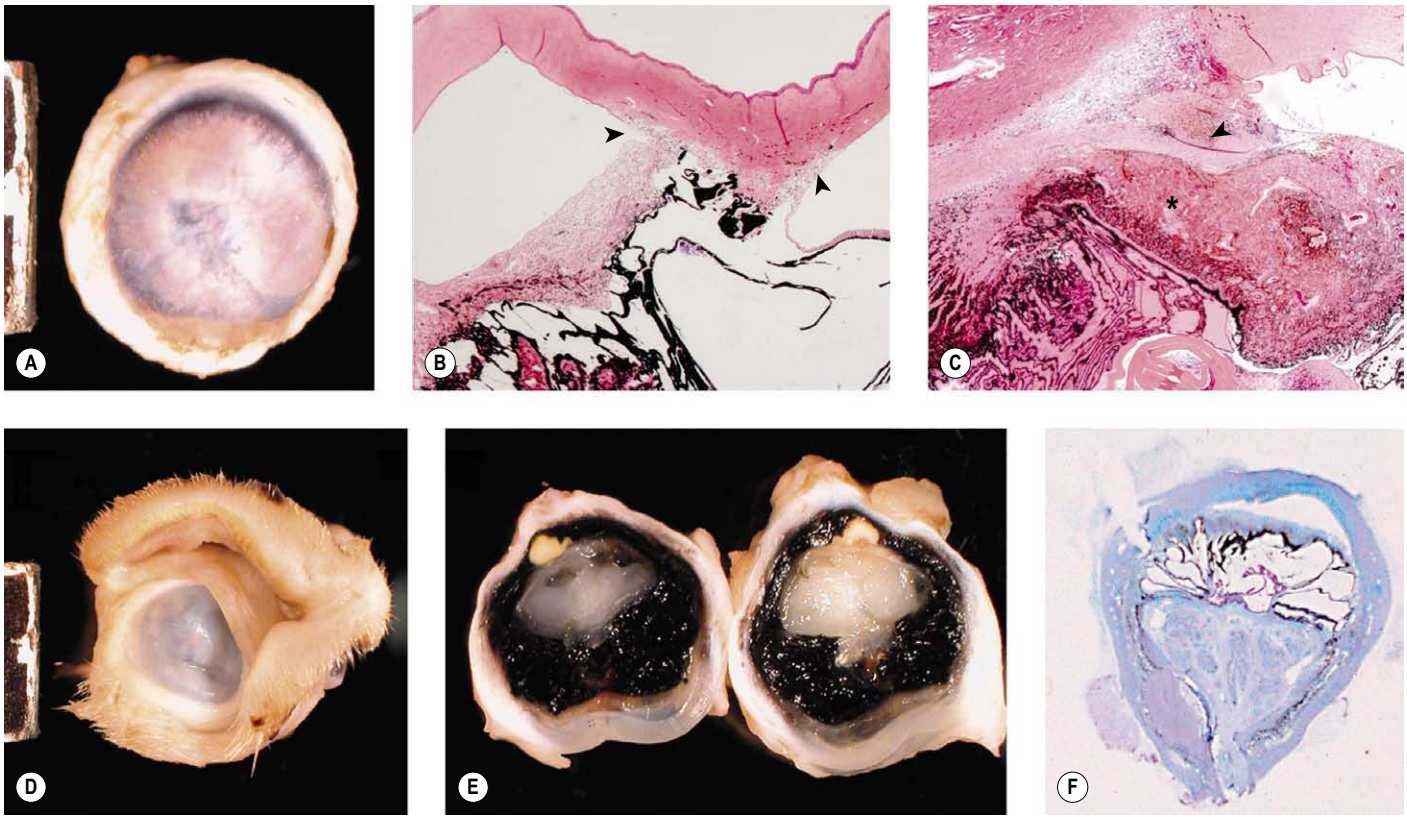


Figure 5.25 Phthisis bulbi. (A) Gross photograph of a phthisical feline globe. (B) Photomicrograph of the same globe showing anterior synechia (arrows) and distortion of the anterior uvea. (C) Photomicrograph of a phthisical canine globe showing fibrovascular proliferation in the anterior chamber (arrow), but not in the anterior uveal tissues (*). (D,E) Gross photographs of a phthisical feline globe. (F) Subgross photomicrograph of the same globe showing collapse of the tissues around the wrinkled lens capsule and fibrosis of the inner aspects of the globe with relative sparing of the uveal tract (Alcian blue PAS).

- This neoplasm lacks a rich blood supply
- The neoplastic cells are predominantly pleomorphic round-cells, with a large nucleus-to-cytoplasm ratio, hyperchromatic nuclear features, and abundant mitoses

- Immunohistochemical features of round-cell variant FPTOS:
  - These tumors are not positively labeled for vimentin, smooth muscle actin, or cytokeratin
  - They stain with a complex staining pattern and are not easily categorized as T-cell or B-cell lymphoma.
- Prognosis
  - Insufficient follow-up information is available to allow accurate prognostication
  - Local recurrence and systemic spread are both seen, but the features that are predictive of a poor prognosis have not been elucidated
  - Primary ocular or systemic lymphoma
    - Lymphoma in feline globes is often seen in conjunction with inflammation. It is likely that the round-cell variant of feline post-traumatic sarcoma represents an example of lymphoma developing in association with the chronic inflammation that may ensue following trauma to the globe.

Post-traumatic osteosarcoma and/or chondrosarcoma (Figs 5.28 and 5.35)

There are 29 cases of osteosarcoma or chondrosarcoma FPTOS in the COLPOW collection representing 10% of the total FPTOS cases.

- Morphologic features of FPTOS-osteosarcoma type (Figs 5.35, 5.36):
  - The distribution of tumor is diffuse within the globe
  - All cases have lens rupture
  - Features suggestive of lens epithelial cell origin are variably present
  - The tumor may demonstrate areas of chondromatous differentiation or, as in four cases, contain only cartilaginous differentiation and no osteoid
- A lack of follow-up information makes it difficult to predict the biological and clinical behavior of these tumors.

Prophylactic enucleation of traumatized feline globes (Fig. 5.33)

Approximately 8% of feline globes in the COPLOW collection, where it could be determined that the globe was removed primarily for prophylactic reasons, had an early spindle cell variant FPTOS

- This percentage does not take into consideration the long latency period that often precedes the development of a clinically apparent neoplasm
- The prophylactic removal of feline globes with trauma and lens capsule rupture should be considered, particularly if vision has already been lost and long-term diligent monitoring is unlikely.

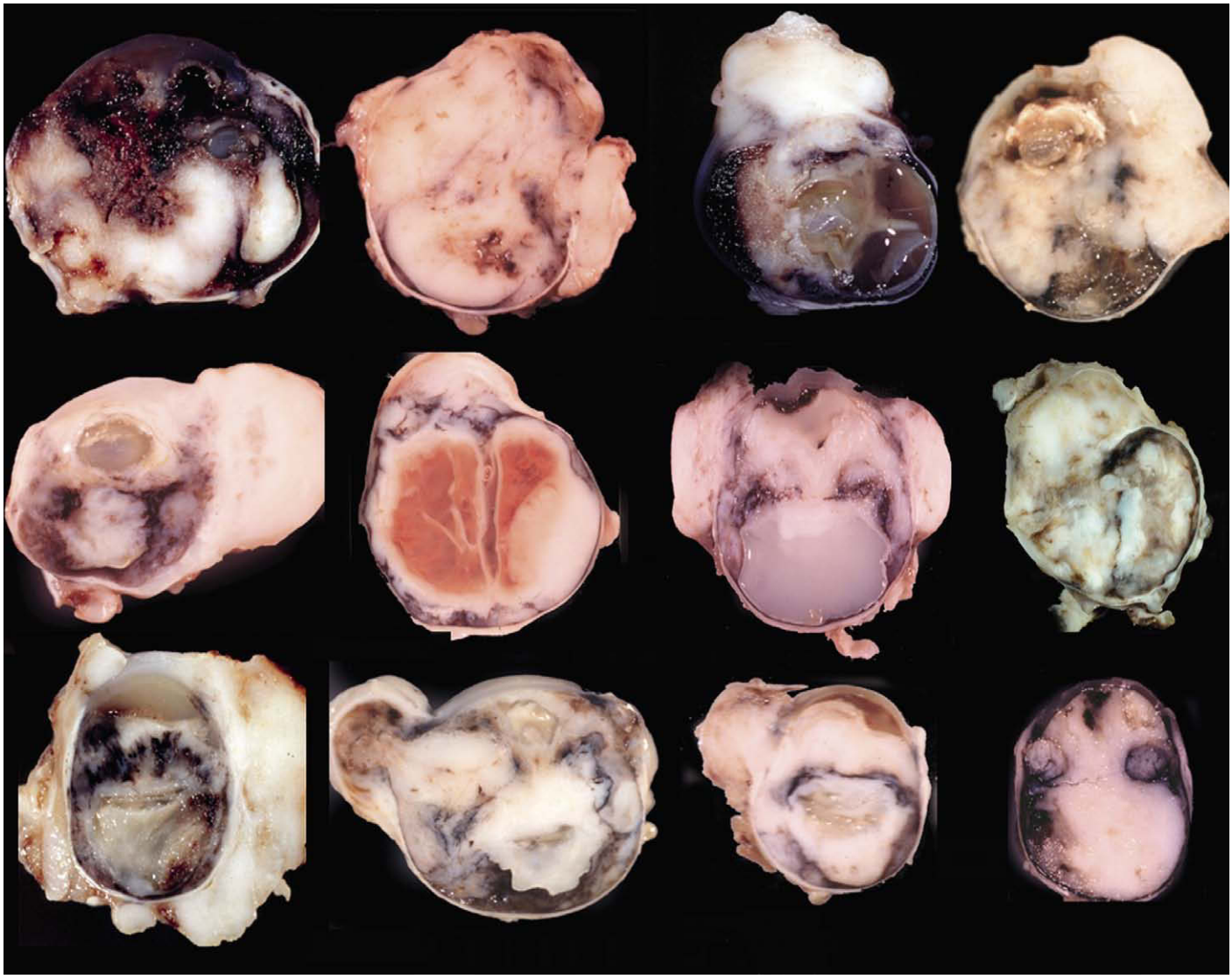


Figure 5.26 Feline post-traumatic ocular sarcoma, spindle cell variant. This montage of 12 gross feline globes shows the morphological variations of the spindle cell variant of feline post-traumatic ocular sarcoma.

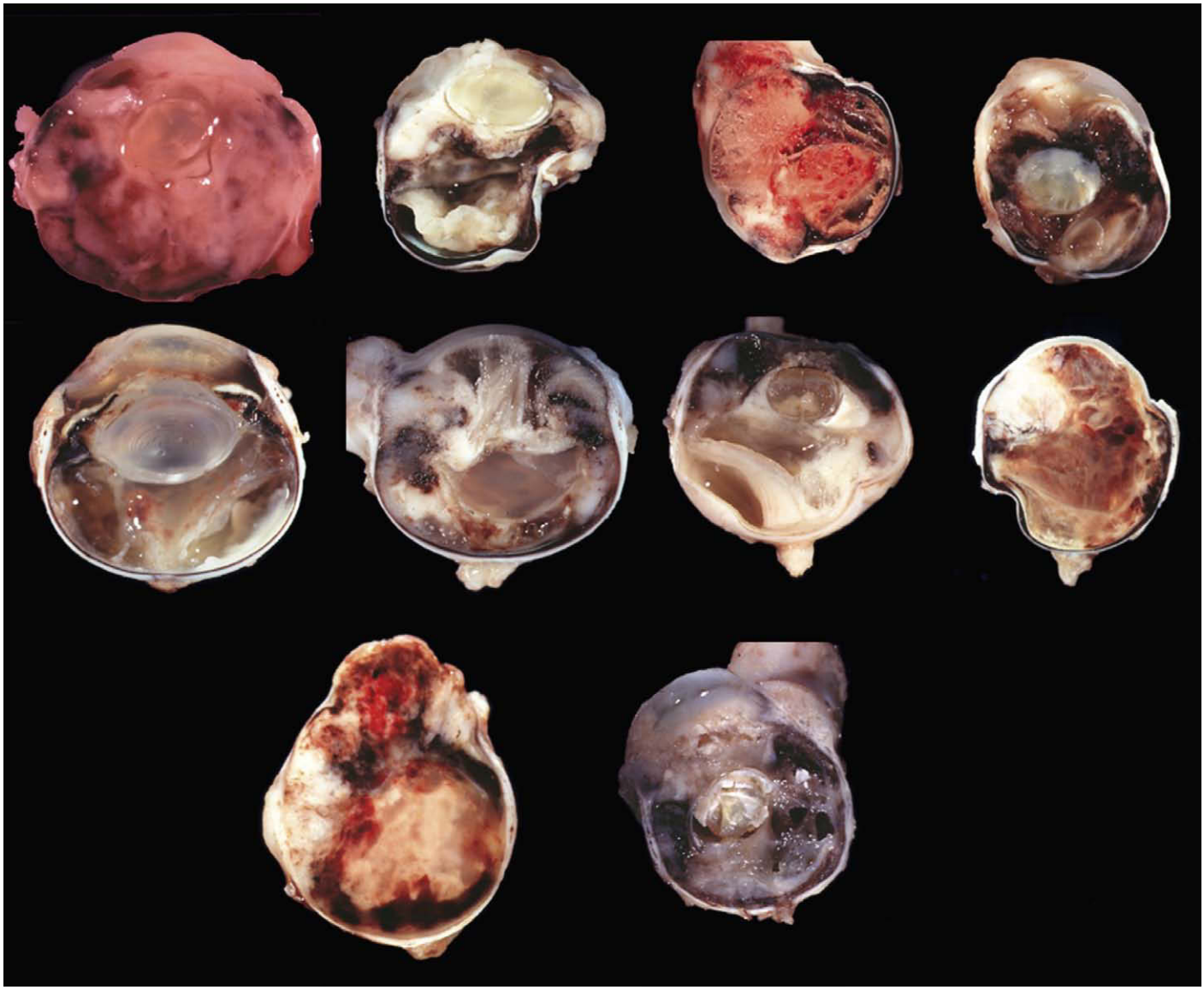
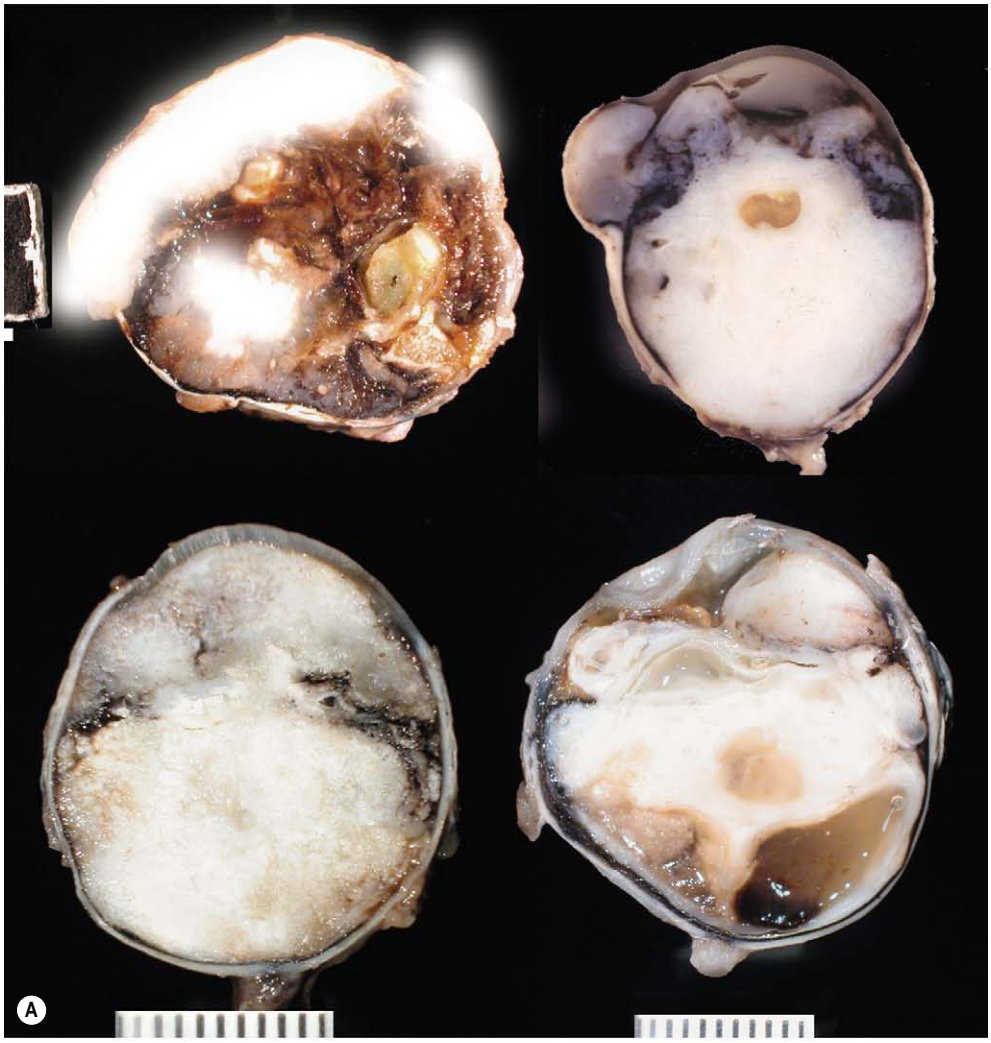


Figure 5.27 Feline post-traumatic sarcoma, round-cell variant. This montage of 10 feline globes shows the morphological variations of round-cell variant of feline post-traumatic ocular sarcoma.



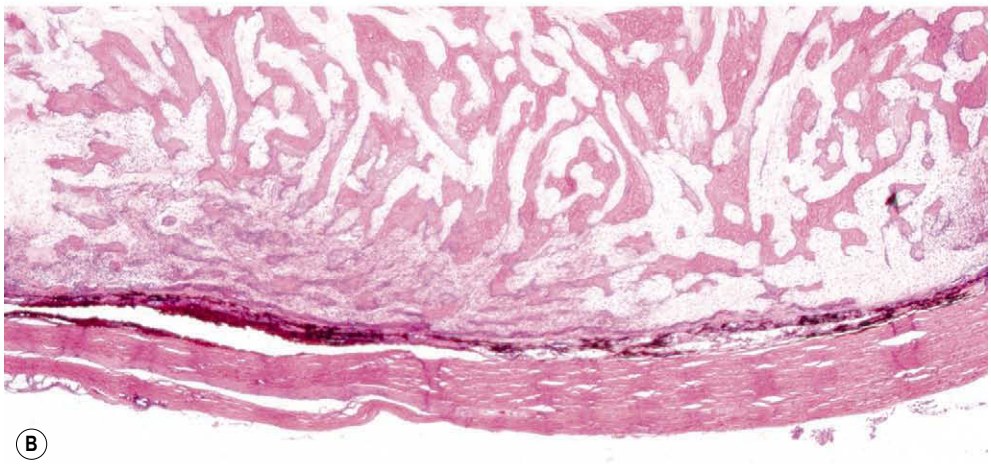


Figure 5.28 Feline post-traumatic ocular sarcoma, osteosarcoma. (A) Four feline globes showing the morphological variations of the osteosarcoma/chondrosarcoma variant of feline post-traumatic ocular sarcoma. (B) Low magnification photomicrograph showing neoplastic osteoid deposition internal to the pigmented choroid.

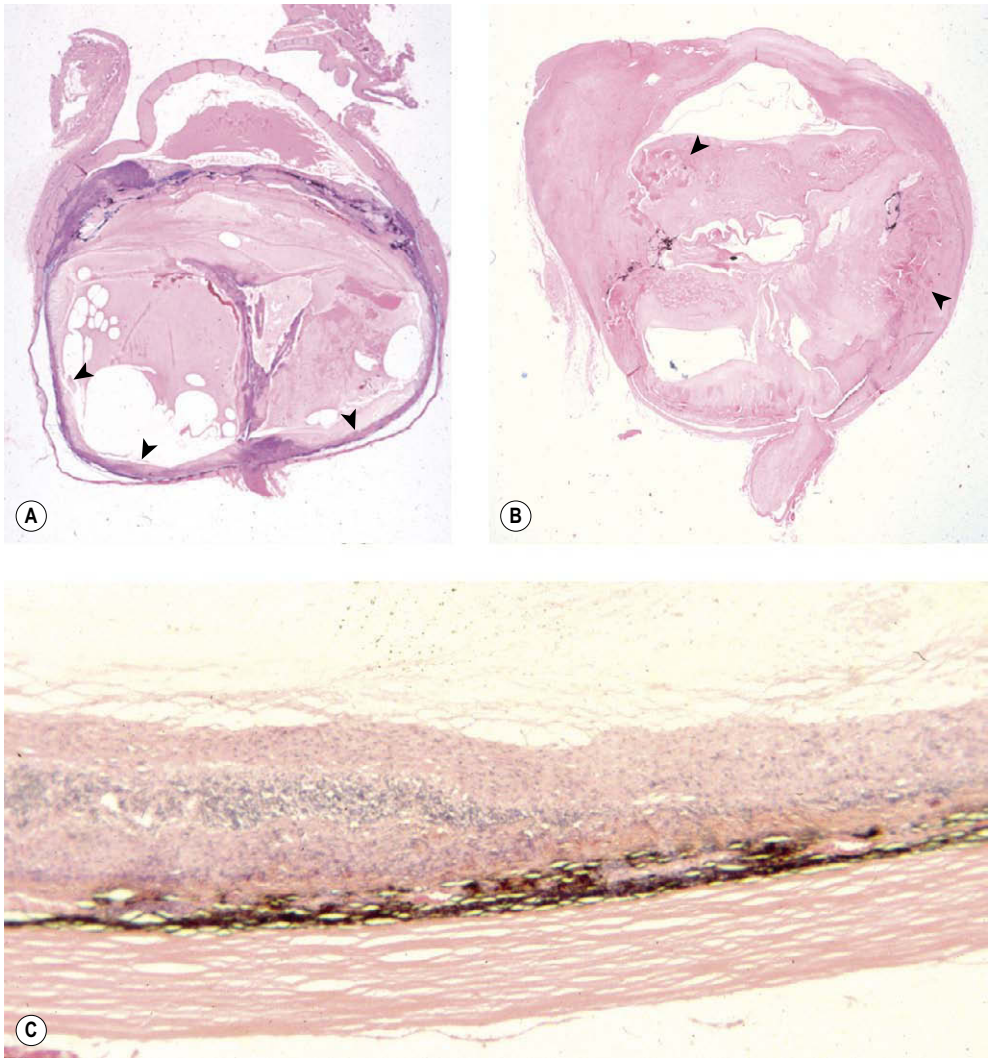


Figure 5.29 Feline post-traumatic ocular sarcoma, distribution in the globe. (A,B) Subgross photomicrographs showing the typical distribution of the spindle cell variant of feline post-traumatic ocular sarcoma. The neoplastic tissue is dispersed circumferentially around the globe as is pointed out by the arrows in (A). The arrows in (B) point to areas of osseous metaplasia within the tumor. (C) Low magnification photomicrograph showing a carpet of neoplastic tissue just internal to the choroid.

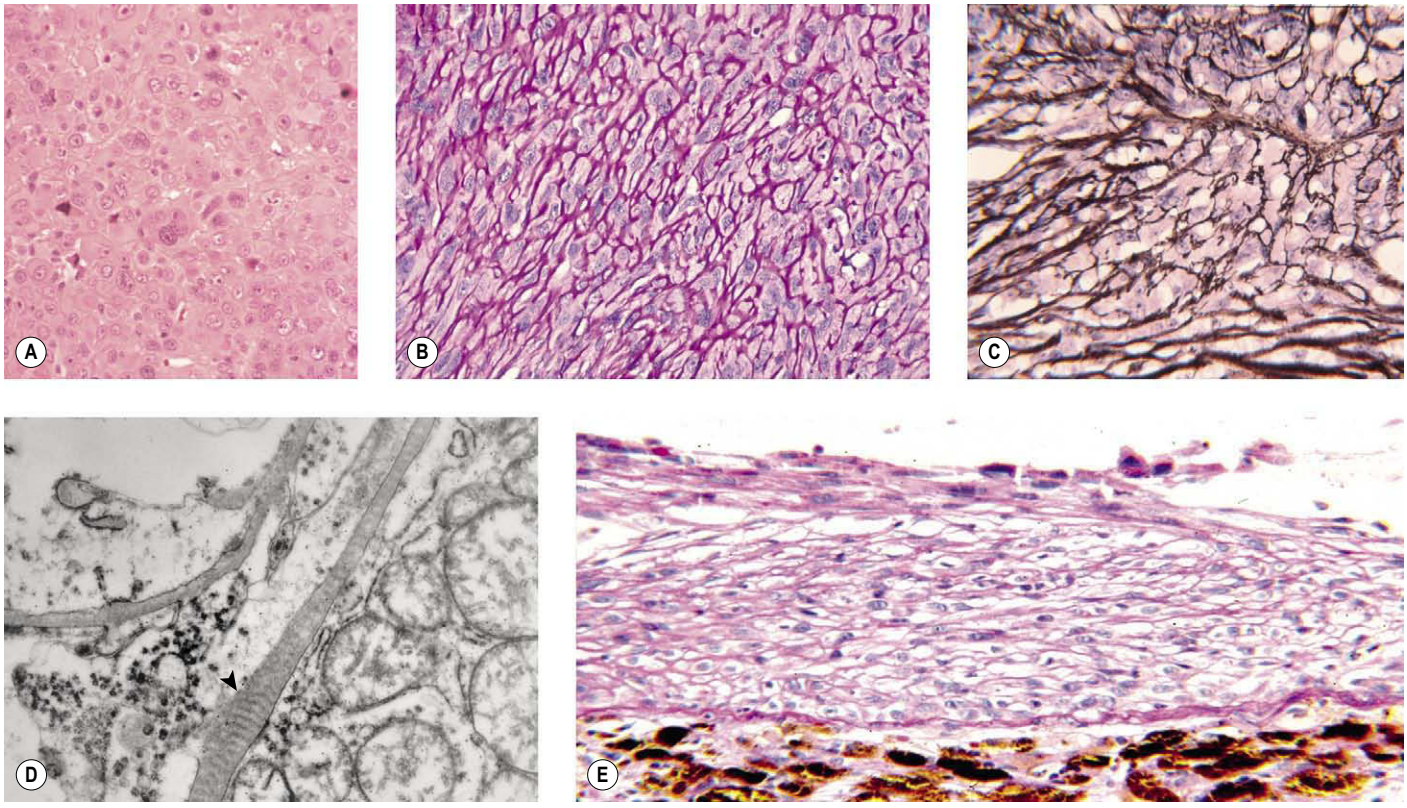


Figure 5.30 Spindle cell variant post-traumatic ocular sarcoma, histopathology. (A) Photomicrograph showing an anaplastic spindle cell variant tumor. (B,C) Photomicrographs highlight the basal lamina-like matrix between individual tumor cells with the PAS stain (B) and the Jones basement membrane stain, a silver stain (C). (D) A transmission electron micrograph showing the same matrix with broad, banded collagen fibers (arrow), a feature common to lens capsule. (E) Neoplastic cells internal to the choroid with less distinct PAS-positive staining around individual tumor cells.

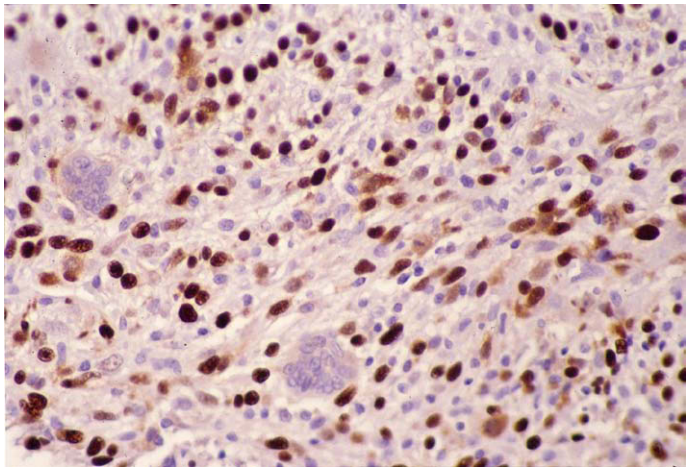


Figure 5.31 p53 Staining in spindle cell variant post-traumatic ocular sarcoma. Immunohistochemistry of a spindle cell variant feline post-traumatic ocular sarcoma shows intranuclear p53-positive staining. The multinucleate cells show no staining.

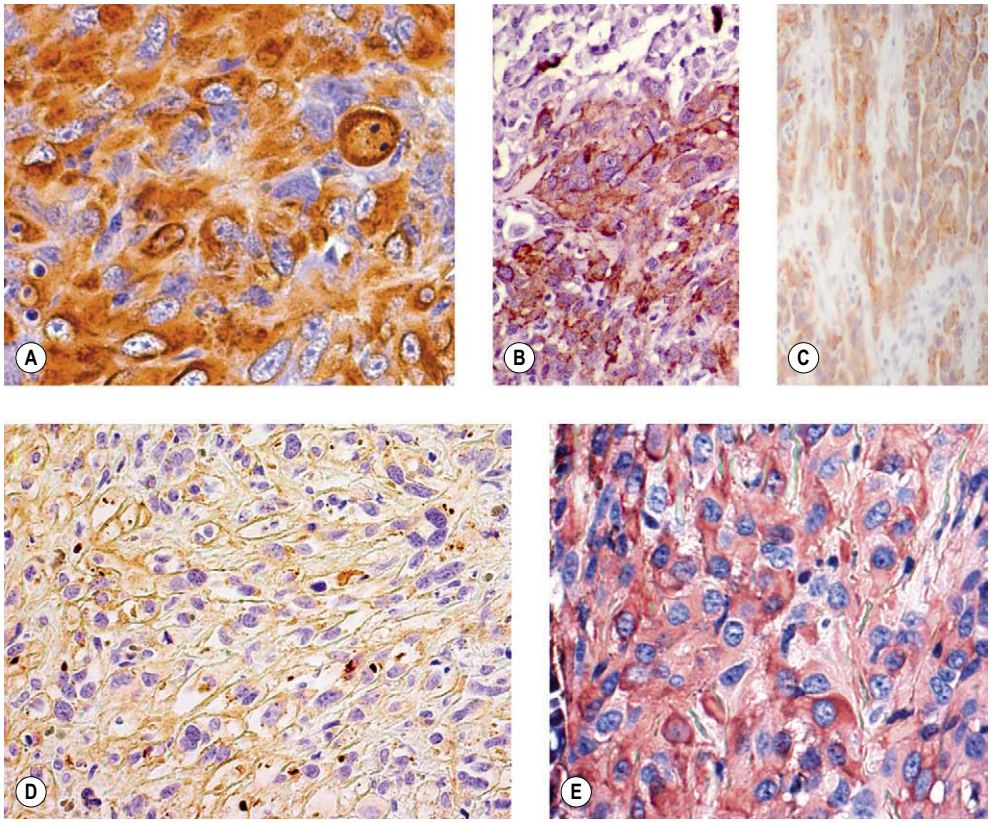


Figure 5.32 Spindle cell variant post-traumatic ocular sarcoma, immunohistochemistry. (A) Vimentin-positive staining typical of a mesenchymal tumor. (B) Smooth muscle actin-positive staining, similar to metaplastic lens epithelial cells seen in posterior capsular opacification after cataract surgery. Less that half of these tumors stain positive with smooth muscle actin. (C) Cytokeratin-positive staining. About 25% of these tumors stain positive with cytokeratin. (D) Collagen IV-positive staining of the extracellular matrix is consistent with basal lamina or lens capsular collagen. (E) α-Crystallin A-positive staining. This is the most common crystallin protein of the lens epithelium. (Reproduced with permission from Zeiss C J, Johnson E M, Dubielzig R R 2003 Feline intraocular tumors may arise from transformation of lens epithelium. Vet Pathol 40:355–362.)

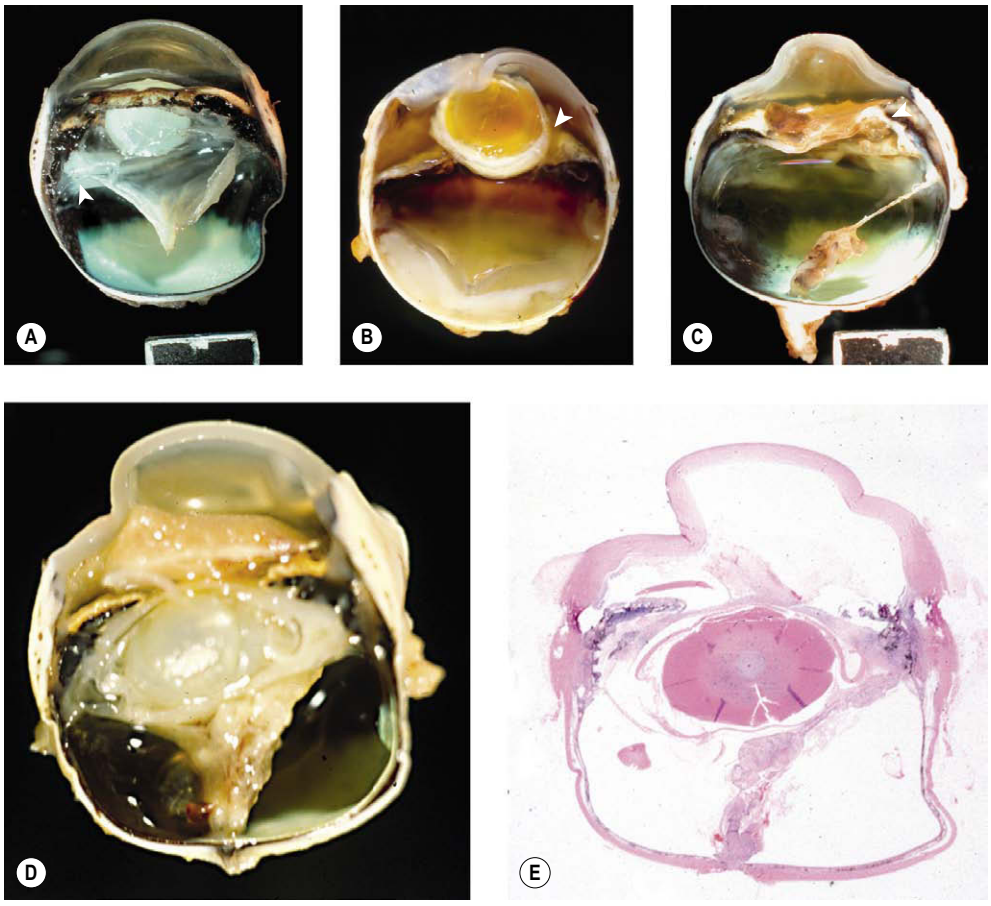


Figure 5.33 Early spindle cell variant post-traumatic ocular sarcoma. (A–C) Early feline post-traumatic sarcomas in globes that were removed for prophylactic reasons. The arrows point to the areas of early neoplastic proliferation in each globe. (D,E) Gross globe and subgross photomicrographs showing an early post-traumatic sarcoma adjacent to the ruptured lens.

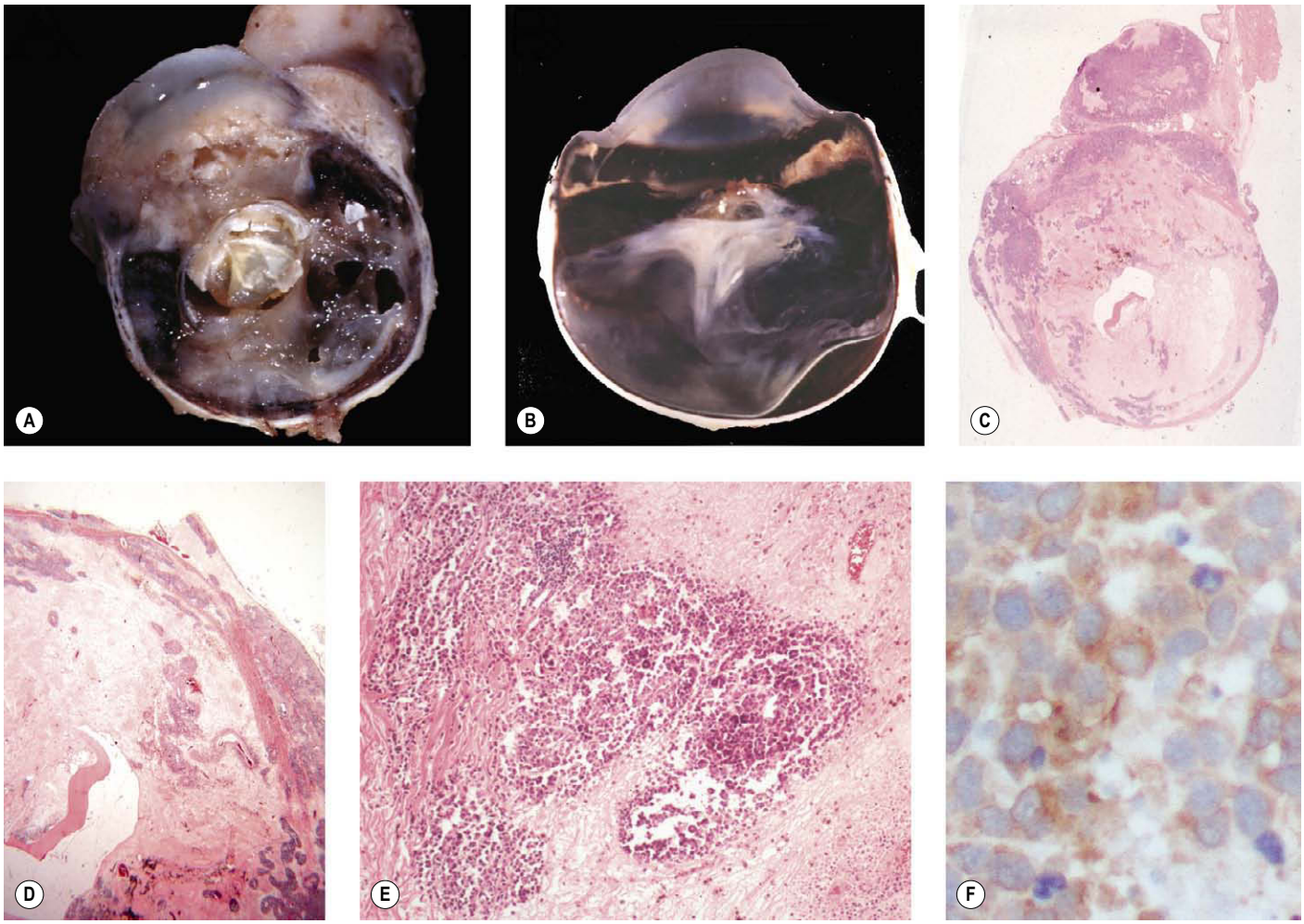


Figure 5.34 Round-cell variant post-traumatic sarcoma. (A,B) Two gross images of a round-cell variant feline post-traumatic sarcoma. Advanced disease (A) and early disease (B). (C) Subgross photomicrograph showing the distribution of neoplastic tissue circumferentially within the globe similar to the spindle cell variant. (D) Higher magnification of (C). (E) Neoplastic round-cells survive around blood vessels in a sea of necrotic cells. (F) Immunohistochemistry (CD79a for B-cells) confirms the diagnosis of round-cell variant, but it is still unclear if these tumors are of B-cell or T-cell lineage.

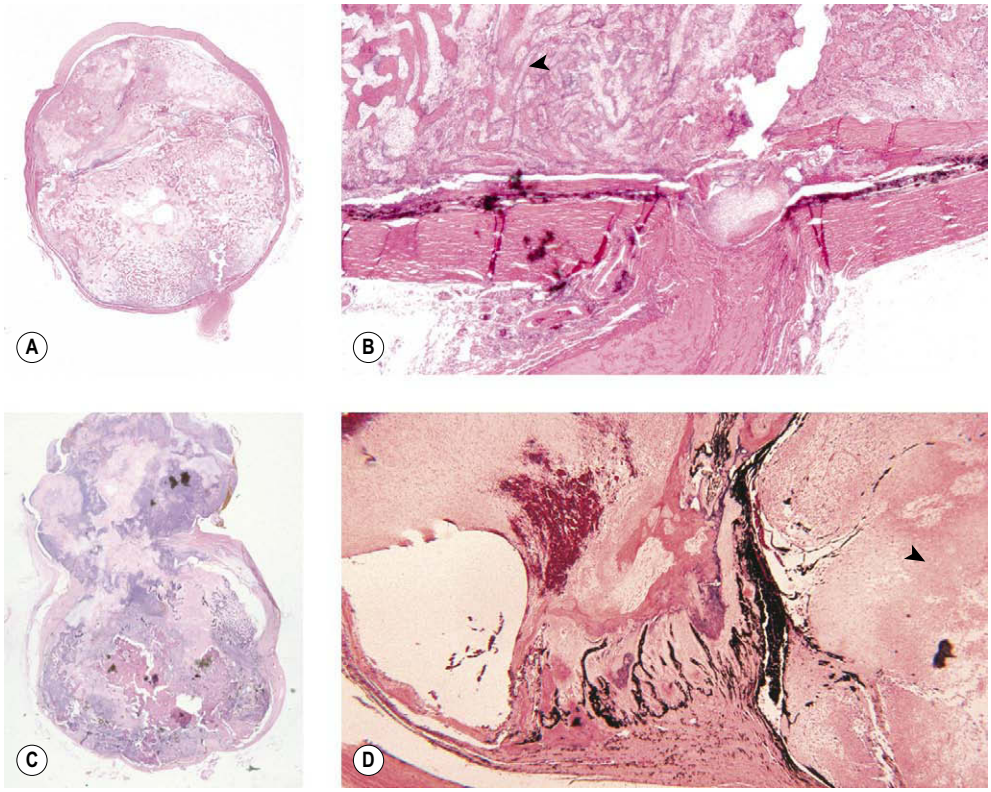


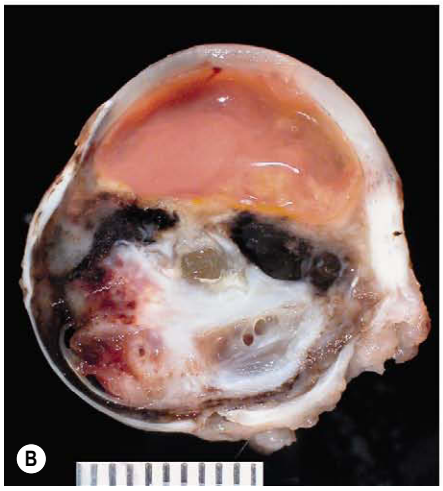
Figure 5.35 Feline post-traumatic ocular sarcoma, osteosarcoma variant, histopathology. (A,C) Subgross photomicrographs of osteosarcoma/chondrosarcoma variant of feline post-traumatic ocular sarcoma (A, H&E; C, Alcian blue PAS). (B,D) Low magnification photomicrographs showing neoplastic osteoid deposition (arrows) within affected globes.

Comparative Comments

Rarely, neoplastic or tumor-like proliferations have been described for the traumatized human eye, but no true counterpart for FPTOS has been observed to date.

- Ocular pleomorphic adenocarcinoma is an extremely rare intraocular malignancy in humans that occurs in previously traumatized globes. This tumor is also seen in dogs, as discussed in Chapter 9
  - This neoplasm is thought to be derived from ciliary body epithelial cells
- In contrast to the canine and feline lens epithelium, lens epithelial cells in humans have a more limited proliferative response to lens capsule rupture, both following trauma and post-operatively following cataract surgery
  - In humans, although lens epithelial cells may proliferate and migrate, they retain their contact with the remnants of the lens capsule
- Long-established dogma, in the human ophthalmic pathology experience, holds that lens epithelial cells do not spontaneously give rise to neoplasia. However, our experiences that support a lens epithelial cell origin for many cases of FPTOS challenge this dogma.





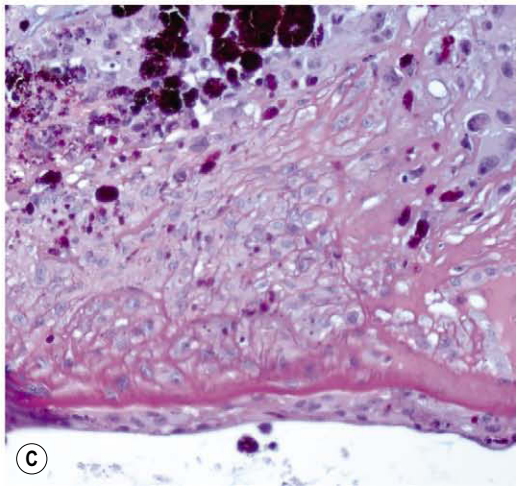


Figure 5.36 Post-traumatic sarcoma seen early. (A) DSH, 1 year old: clinical photograph, taken after ocular trauma, showing cataract in a small, anteriorly luxated lens. Trauma resulted in lens resorption with only nucleus attached to the inferior iris (arrow). The detached retina was also observed. The cat developed feline post-traumatic sarcoma years after this clinical photograph was taken. (B) Gross photograph showing post-traumatic sarcoma 11 years after Figure 5.36A was taken. (C) Photomicrograph showing post-traumatic sarcoma, spindle cell variant (PAS stain).

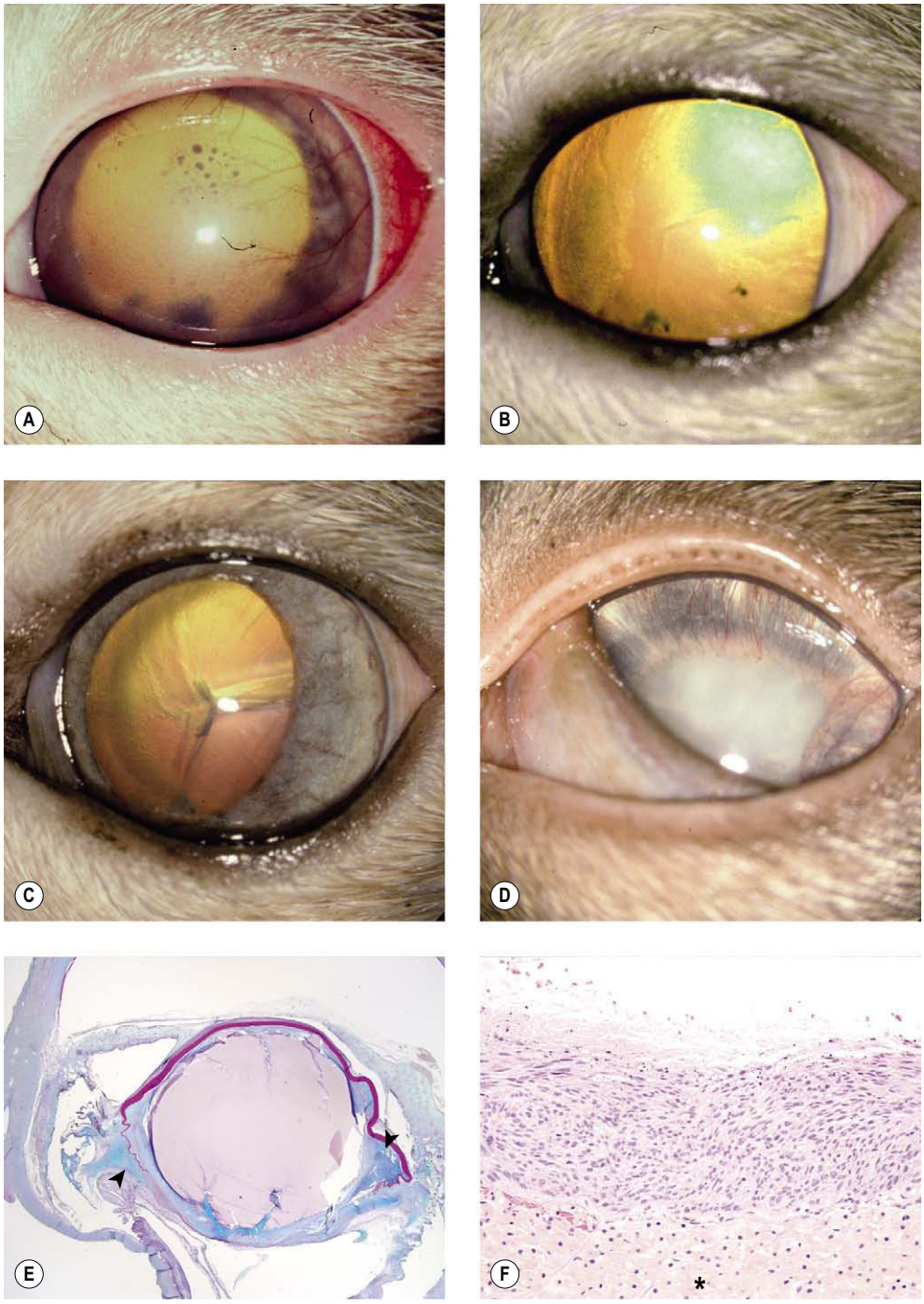


Figure 5.37 Uveitis diagnosed as *Cryptococcosis* and *Toxoplasmosis* in a cat leading to post-traumatic sarcoma. (A) Siamese, 7 years old: left eye represents the bilateral anterior uveitis. Chorioretinitis was also present. Based on serology, *Cryptococcus* and *Toxoplasmosis* was diagnosed as the etiology. (B) Same cat as in (A) 2 months after treatment: mild diffuse cortical opacities are developing. (C) Same cat as in (A,B) 2 weeks later: the cortical opacities are increasing in density. (D) Same cat as in (A–C) 3 years later: the lens appears hypermature. Posterior synechia is present with vessels extending from the iris onto the lens. Iris bombe is present and is especially obvious temporal. Histopathology demonstrated an early lens induced sarcoma. (E) Low magnification photomicrograph of the same eye, with Alcian blue PAS stain, showing hypermature cataract broad synechia and thick cellular and fibrous tissue around the wrinkled lens capsule (arrows). (F) Photomicrograph showing neoplastic spindle cells from the same eye internal to the tapetum (*).

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Chapter 6

Diseases of the orbit

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Diseases of the orbit may originate within the structures of the bony orbit (that vary between species), or in the orbital soft tissues, including the globe, extraocular muscles, and variable secretory tissues such as the zygomatic salivary gland, as well as the rich neurovascular supply to these tissues. However, many diseases affecting the orbit represent the extension of inflammatory or neoplastic processes from adjacent tissues. Thus, important anatomic considerations in the diagnosis of orbital disease also include the proximity of the oral and nasal cavities, the para-nasal sinuses, muscles of mastication, and brain.

INFLAMMATORY DISEASE OF THE ORBIT

Orbital inflammatory disease is relatively common

- In the COPLOW collection, orbital inflammation is usually diagnosed in conjunction with panophthalmitis, in globes that were enucleated because of intraocular inflammation that had concurrent orbital inflammation
- This combination is most common in dogs and there are 84 cases in the COPLOW collection.

Orbital cellulitis or abscess secondary to tooth root inflammation (Fig. 6.1)

- Most common in dogs, rabbits, chinchillas, and horses
  - Periodontitis extending to the root apex
  - Pulpitis due to exposure of the root canal from trauma or caries, which occurs less frequently in domestic animal species than in humans

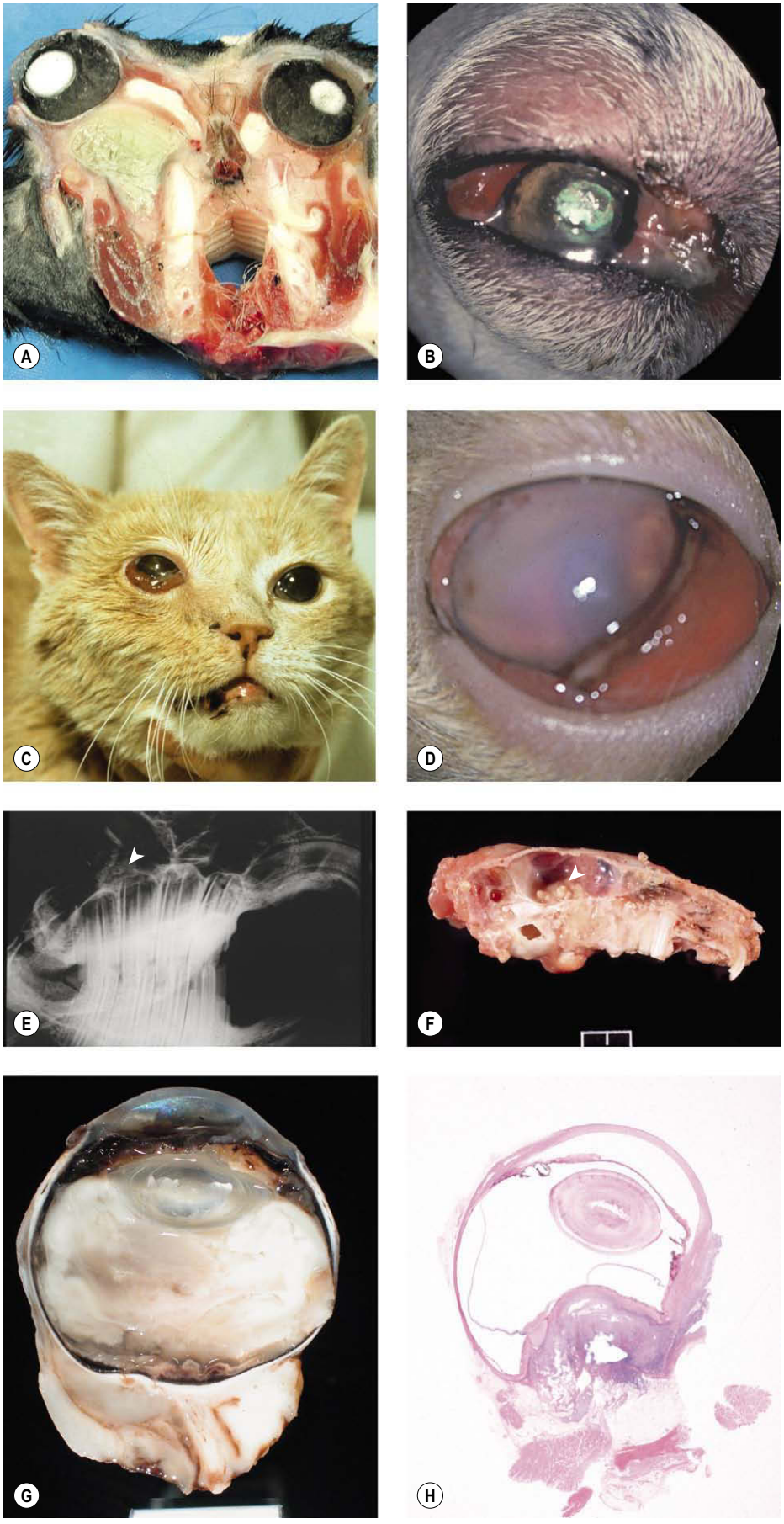


Figure 6.1 Orbital abscess. (A) Gross photograph of sectioned rabbit skull with orbital abscess related to dental disease. (B) Golden Retriever, 5 years old: periocular swelling and serosanguineous discharge was due to a dental abscess. (C) DSH, 8 years old: this globe is exophthalmic, the conjunctiva is hyperemic and chemotic, and the right side of the face is swollen secondary to a dental abscess. (D) DSH, 5 years old: the third eyelid is hyperemic and prolapsed over the exophthalmic globe. Exposure keratitis resulted in poor visualization of the anterior segment. (E) Rabbit skull radiograph showing periapical bone lysis (arrow). (F) Gross photograph of the skull in (E) showing abscess extending into the calvarium (arrow). (G) Gross photograph of canine globe showing an orbital abscess in the posterior pole as well as panophthalmitis. (H) Subgross photomicrograph of a similar canine globe with abscess in the orbital tissues at the posterior pole.

- Radiographic evidence of osteolysis at the tooth root apex, particularly involving the caudal maxillary tooth roots
- Consider the possibility of trauma and iatrogenic spread of infection to the orbit during dental procedures
  - There are six cases in the COPLOW collection in which orbital suppurative inflammation and panophthalmitis occurred shortly following a dental procedure.

Orbital inflammation secondary to deep orbital soft tissue injury (Fig. 6.2)

Most of these cases are presented because there is panophthalmitis and the orbital inflammation itself is not well-characterized, either clinically or histopathologically.

Penetrating injury from the oral cavity

- Most severe disease is seen in the inferior tissues of the orbit, dependent to the globe
- Fistulous and suppurative processes generally characterize the inflammatory response
- The degree of fibrosis is variable but, in some cases, can dominate the pathology
- Foreign bodies can be challenging to identify and are rarely found on histopathology. Orbital foreign bodies are more commonly identified in dogs than in cats (82 dogs versus 12 cats in the COPLOW collection)
  - Plant material is most common
    - 41 documented cases in dogs
    - Four documented cases in cats
  - Porcupine quills may penetrate the orbit directly or migrate from adjacent tissues. There are two such cases in the COPLOW collection.

Penetrating injury from external trauma, including bite-wounds

Such injury is more likely to occur in species such as the dog and cat that have a relatively 'open' bony orbit.

- Most severe disease is present within the lateral or superior orbit, rather than inferior orbit
  - If the wound is lateral, then it is less likely to be sampled with the standard vertical section of the globe. Special instructions from an alert clinician are essential if the primary lesion is to be located
- Other findings similar to penetrating injury from the oral cavity.

Orbital inflammation associated with specific organisms

Mycotic infections

Infection of the orbit may result from hematogenous spread in disseminated, systemic mycoses, or by extension of local infection from the nasal cavity, paranasal sinuses, or from the globe. The systemic mycoses are considered in greater depth in Chapter 9.

Blastomyces dermatitidis

There are five cases in the COPLOW collection in which a diagnosis of blastomycosis was made from orbital biopsy specimens.

- Four in dogs and one in a cat.

Cryptococcus neoformans

There are three cases in the COPLOW collection, in which the diagnosis was made from orbital biopsy specimens.

- Two in cats and one in a dog
- The canine case had concurrent malignant sarcoma in the orbit.

Coccidioides immitis

There are two canine cases represented in the COPLOW collection, both submitted from the South-western United States.

Candida *spp.*

There are two feline cases of localized orbital candidiasis in the COPLOW collection.

Aspergillus *spp.*

There are three canine cases of orbital aspergillosis in the COPLOW collection, all of which were associated with nasal aspergillosis. This is consistent with previously published reports.

Although not represented in the COPLOW collection, feline orbital aspergillosis has been reported in the literature.

- Affected cats may or may not show clinical evidence of disease in the paranasal sinuses or nasal cavity
- There is an apparent breed predisposition for Persian cats.

Bacterial infections

Bacteria were observed in specimens from 15 cases in the COPLOW collection that had orbital inflammation. Nine canine cases, three rabbits, one cat, one horse and one chinchilla.

- In none of these cases was the identity of the bacterial organism established. This may reflect a failure to submit samples for microbiological culture, or difficulty in isolating organisms due to specific culture requirements.

Parasitic infestations

Canine episcleral onchocercosis (Fig. 6.3)

- This disease of emerging importance is most common in Mediterranean Europe, with reports from Greece, and lesser numbers from Hungary and Germany
  - In the European cases, the morphologic features of adult worms have been reported as being consistent with *Onchocerca lupi* (from wolves). However, this is controversial because nucleotide sequences for this canine form appear to be unique within the genus, and this canine disease may represent host switch and site shift that has resulted in a new *Onchocerca species*
- There are 12 cases in the COPLOW collection from dogs in North America
  - All originated in California or neighboring Western states
  - The parasites involved have previously been identified as *Onchocerca lienalis* but this remains controversial, as the definitive identity of the parasite has not yet been established
    - Cattle are the definitive host for *Onchocerca lienalis*; the adult parasites live in the gastrosplenic ligament
    - *Onchocerca* spp. have a relatively narrow host range, and patent infection (as the presence of adult male and female worms, with microfilaria within the adult female worms in the orbital tissue suggests) would only be expected if dogs, or a closely related species were the definitive host

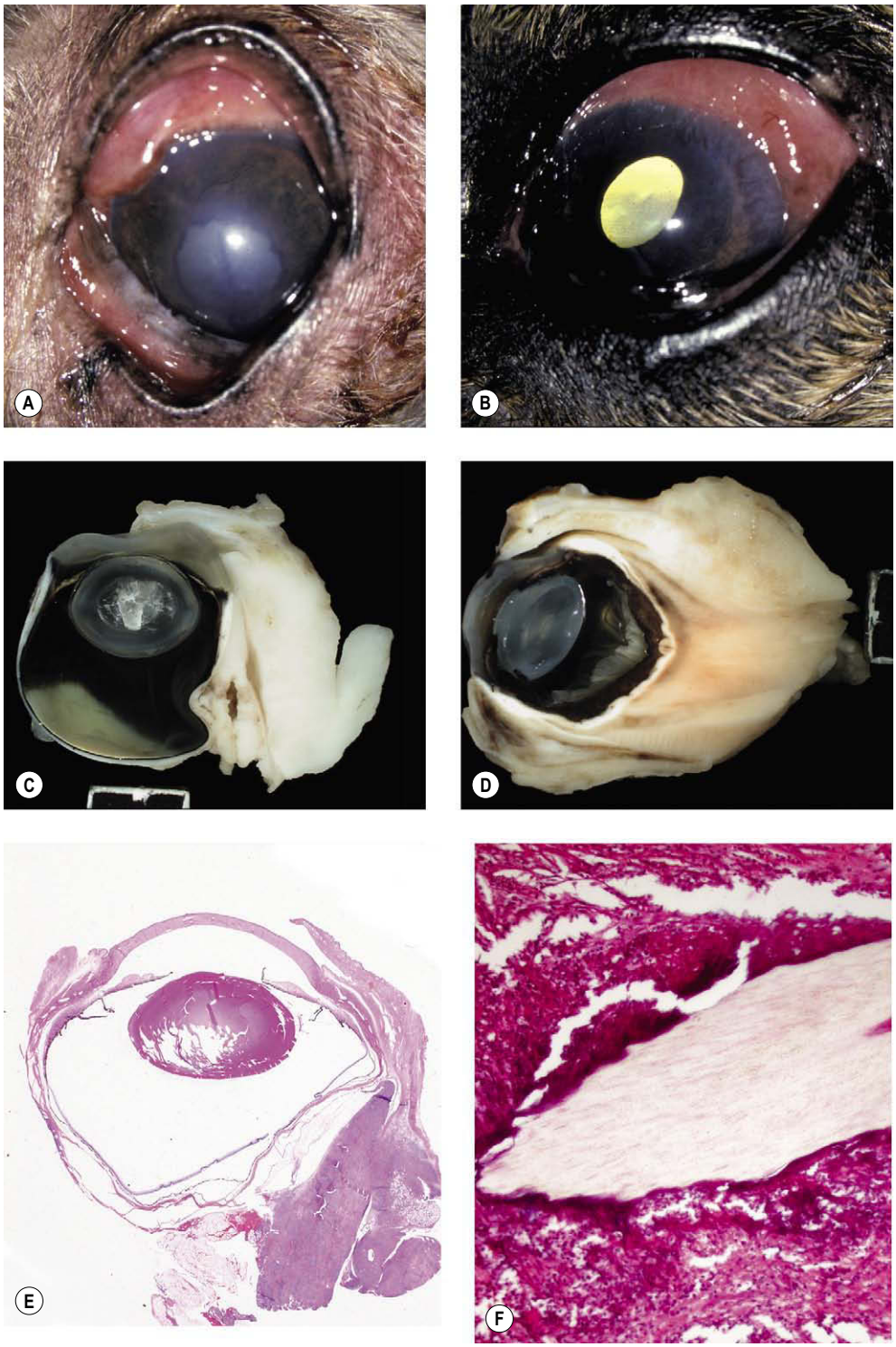


Figure 6.2 Orbital and episcleral inflammation. (A) Miniature Poodle, 10 years old: the exophthalmic globe has severe conjunctival hyperemia, corneal edema and a dense cataract. Zarfoss KM, Dubielzig RR, Eberhard ML, and Schmidt KS. *Canine ocular onchocerciasis in the United States: two new cases and a review of the literature.* Vet. Ophthal. 8: 51–57, 2005. (B) English Bulldog, 5 years old: the conjunctiva and sclera are hyperemic and thickened. Adjacent cornea is edematous and vascularized in this exophthalmic globe. (C,D) Gross photographs of canine globes showing orbital soft tissue inflammation and fistulous tracts. (E) Subgross photomicrograph of a canine globe showing orbital fibrosis with suppurative inflammation. (F) Photomicrograph of the episcleral tissues from a dog showing a porcupine quill within an inflammatory fistula.

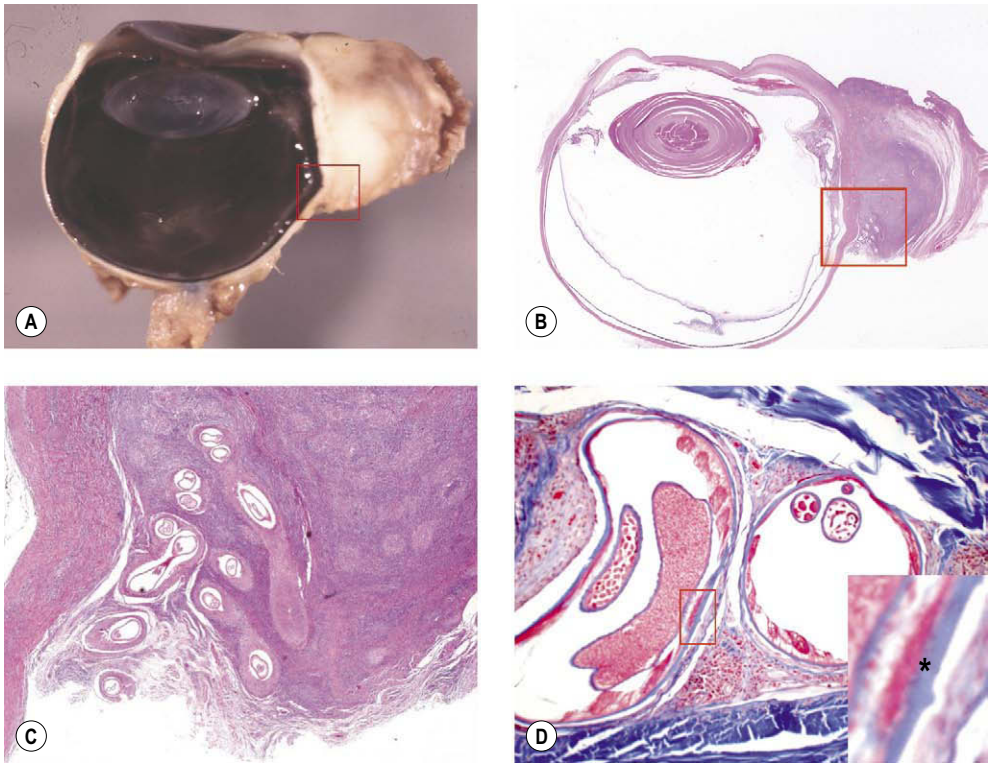


Figure 6.3 Canine orbital *Onchocerca*. (A,B) Gross photograph and subgross photomicrograph showing a proliferative nodule in the orbit and bulbar conjunctiva associated with infestation by the nematode parasite *Onchocerca* sp. (C) Higher magnification photomicrograph, of the boxed area in (A,B) showing nematodes within granuloma-lined clefts in the orbital episcleral tissue of a dog. (D) Photomicrograph showing an adult female nematode. The inset shows a circumferential ridge (*), which is characteristic of *Onchocerca*.

- The clinical manifestations of canine ocular onchocercosis
  - Single or multiple, raised, red lesions seen on the bulbar conjunctiva, with chemosis, erythema, and periocular swelling
  - More chronic cases demonstrate red, nodular, 2 mm to 2 cm mass lesions
  - Exophthalmos, protrusion of the nictitans, or anterior segment involvement may be observed clinically. The latter may include corneal edema and peripheral neovascularization, and anterior uveitis
  - Two of the cases in the COPLOW archive had no clinical signs attributable to the infestation. In these dogs, ocular onchocerciasis was an incidental finding following enucleation for uveal neoplasia
- Morphological features of canine ocular onchocercosis
  - There is a nodular infiltrative lesion in the substantia propria of the conjunctiva, extending into the episcleral tissue and orbital fascia
  - Granulation tissue admixed with eosinophils, lymphocytic inflammation and macrophages
    - It is not essential to find eosinophils in the infiltrate
  - In the posterior aspect of the subconjunctival mass lesions and extending all the way around the episcleral tissues, there are cavities containing adult male and female parasites, surrounded by a pure population of epithelioid macrophages
  - Male and female worms are often seen together, and the females contain microfilaria
- Morphologic features useful for the identification of *Onchocerca* spp.
  - These worms are easily identified as filarial nematodes because they have an obvious cuticle and have coelomyarial musculature, as well as digestive and reproductive system structures
  - The adult females are easily recognizable as filarial worms because they contain microfilaria

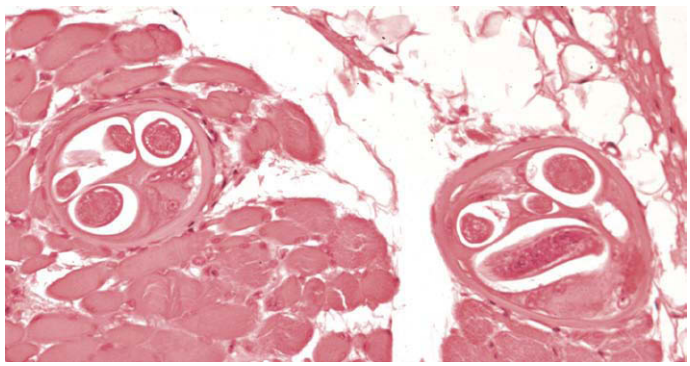


Figure 6.4 Trichinosis. Photomicrograph showing *Trichinella spiralis* in the extraocular skeletal muscle from a dog.

  - The following features may help distinguish *Onchocerca* spp. from *Dirofilaria* spp.
    - The cuticle of adult female *Dirofilaria* spp. worms, have ridges that run longitudinally and therefore are only seen when the worms are sectioned in cross-section
    - The cuticle of adult female *Onchocerca* spp. worms consists of two distinct layers with interior striae and, on the exterior surface, ring-like, circumferential ridges which are only seen when the worms are cut in the longitudinal plane.

Infestation of extraocular muscles with Trichinella spiralis *(trichinosis) (Fig. 6.4)*

There are two cases of canine extra-ocular trichinosis in the COPLOW collection.

- Both cases were in dogs with clinical histories of generalized wasting and fever that were suggestive of systemic disease.

Comparative Comments

The spectrum of inflammatory diseases of the orbit encountered in human pathology differs rather markedly from that seen in the veterinary pathology laboratory. Orbital cellulitis in humans is most commonly caused by extension of an inflammation from the paranasal sinuses. Its cause includes common bacterial infections, with the most commonly identified organisms being *Staphylococcus aureus, Streptococcus, Haemophilus influenzae*, and other Gram-positive rods. Infection may also incur by endogenous routes, as with bacteremia or septic embolization, and from exogenous sources following trauma. Fungal infections may occur in immunocompromised patients and are usually caused by *Mucor* or *Aspergillus* species. *Echinococcus granulosus* is the most common parasitic cyst seen in the orbit.

Canine extraocular polymyositis (Fig. 6.5)

This diagnosis is generally made based on clinical presentation alone. Extraocular muscle biopsy is seldom performed to support the clinical diagnosis, and there are no cases represented in the COPLOW collection; however, the pathology of the condition has been well described.

- Golden Retrievers are over-represented
- Affected dogs are generally 6–18 months old and more often female than male
- In many cases, an antecedent stressor, such as recent kenneling, surgery or estrus is reported prior to the onset of clinical signs
- The condition is bilateral but not always symmetrical and, in its acute phase, causes exophthalmos, chemosis, and retraction of the upper eyelid without protrusion of the third eyelid
- The muscle pathology is dominated by a lymphocytic infiltrate within the muscle tissue. CD3+ lymphocytes predominate
- Chronic fibrosing extraocular myositis with restrictive strabismus
  - Has been reported in young large-breed dogs and Shar Peis
  - May be unilateral or bilateral
  - Clinical presentation is of rapid onset and progression of enophthalmos and severe ventro-medial strabismus leading to visual impairment
  - May represent a chronic phase of extraocular muscle polymyositis
  - Characterized by fibrosis and lymphoplasmacytic infiltrate restricted to the extraocular muscles.

Comparative Comments

This condition has many features similar to Graves' disease in humans.

- The orbital manifestations of severe ophthalmopathy with exophthalmos in Graves' disease usually begin in adults. Older males are affected more often than younger females, in contrast to the mild form of thyrotoxic exophthalmos

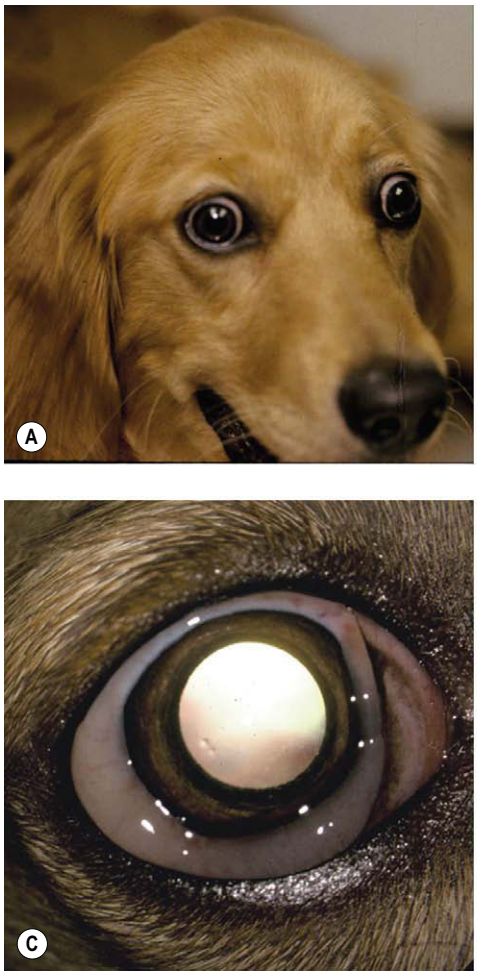


Figure 6.5 Extraocular polymyositis of Golden Retrievers. (A) Golden Retriever, 18 months old: characteristic bilateral axial exophthalmia with increased scleral 'show' is present. (B) Golden Retriever, 10 months old: gross photograph of the brain, eyes, optic nerve and still-connected extraocular muscles showing thickening and pallor in the extraocular muscle tissues. The arrows point to two swollen extraocular muscles. Reproduced with permission from Carpenter JL, Schmidt GM, Moore, FM, Albert DM, Abrams KL and Elner VM. *Canine bilateral extraocular polymyositis.* Vet. Pathol. 26: 510–512, 1989. (C) Golden Retriever, 9 months old: the bilateral exophthalmia was also associated with chemosis and hyperemia of the conjunctiva.

Comparative Comments (continued)

- Patients with this severe form of disease are often hyperthyroid, but patients may be hypothyroid or euthyroid
- The disease is an inflammatory extraocular myopathy, with a predominantly T-cell infiltrate
- In the later stages of disease the affected extraocular muscle tissue may become fibrotic
- Thyroid orbitopathy is the most common cause of unilateral and bilateral exophthalmos in adults. This usually involves extraocular muscles and is characterized by inflammatory enlargement of extraocular muscles and subsequent scarring.

Masticatory muscle myositis

- There is a predisposition for young, large-breed dogs
- May cause exophthalmos, due to displacement of the globe secondary to swelling of pterygoid and/or temporalis muscles that form soft-tissue boundaries of the open, canine orbit
- Subsequent fibrosis of the pterygoid and temporalis muscles may lead to enophthalmos
- Muscle biopsy and detection of serum antibodies against type 2M muscle fibers may be helpful in the diagnosis of masticatory myositis
- Generalized polymyositis and infectious causes of myositis (including neosporosis, toxoplasmosis and leishmaniasis) should be considered in the differential diagnosis of extraocular and masticatory myositis.

Other, poorly characterized, orbital sclerosing conditions

Feline restrictive orbital sarcoma (feline sclerosing pseudotumor) (Fig. 6.6)

There are 10 cases diagnosed in the COPLOW collection.

- This condition has a very characteristic clinical appearance:
  - There is variable exophthalmos, with very pronounced reduction in globe motility
  - Retraction of the upper eyelid contributes further to severe corneal exposure and desiccation, which is often associated with ulcerative keratitis
- Morphologically, the condition is characterized by a mixture of bland spindle cells, associated with variable amounts of extracellular collagen deposition and perivascular infiltration of lymphocytes
  - The spindle cell infiltrate and collagen accumulation extends from the conjunctival substantia propria to the episcleral tissue at the posterior pole of the globe
- Gradual progression, over weeks to months, to involve the second eye is typically reported
- Involvement of the skin, lip, and/or oral mucosa, with pronounced gingival thickening, has also been reported
- The etiopathogenesis of this condition has not yet been elucidated
- Evaluation of the head from cats after euthanasia, reveals bone lysis and neoplastic infiltration of the empty orbit. At the end of life mass lesions are more likely to be a part of the syndrome
- The progressive, nature and the histological appearance of the proliferative lesions are more consistent with a form of fibrosarcoma rather than with a non-neoplastic inflammatory disease.

Comparative Comments

Pseudotumor in humans:

- Categorized as granulomatous, or non-granulomatous
- Sclerosing pseudotumor is a subtype of non-granulomatous pseudotumor
- The hallmark of sclerosing pseudotumor is the early appearance of fibrosis that is out of proportion to the lymphocytic inflammation
  - This is similar to idiopathic restrictive orbital sarcoma or sclerosing pseudotumor in cats.

Canine systemic histiocytosis (Fig. 6.7) (see Ch. 7 for detailed discussion)

There are seven cases with orbital involvement diagnosed in the COPLOW collection: two in Bernese Mountain dogs, three in Labrador Retrievers, and two in other breeds. The three forms of canine histiocytosis that have been described include:

1. Cutaneous histiocytosis, the most benign and localized – this diagnosis has not been made in the COPLOW collection.
2. Systemic histiocytosis, which has been diagnosed in the COPLOW collection.
3. Malignant histiocytosis, the most malignant of the three, based on morphological and biological behavior. Malignant histiocytosis has not been diagnosed in the COPLOW collection.

The morphologic features useful in diagnosing systemic histiocytosis are as follows:

- Solid nodular tumors characterized by sheets of only moderately dysplastic histiocytes, that lack anaplastic features
- Minimal lymphocytic or neutrophilic involvement
- No classical granulomatous nodules
- Evidence of vasocentricity
  - This ranges from histiocytic cells tightly surrounding blood vessels, to blood vessel destruction and obliteration
    - Vasocentric infiltration is considered a very important diagnostic consideration at COPLOW
- Reticulin fibers surrounding the histiocytes.

Systemic histiocytosis may regress spontaneously but often requires aggressive anti-inflammatory chemotherapy

Comparative Comments

Specific causes of non-infectious orbital inflammation in humans include: ruptured dermoid cysts; idiopathic orbital inflammatory disease (pseudotumor); sarcoidosis; amyloidosis and systemic autoimmune vasculitides. The most common of this latter group is Wegener's granulomatosis, characterized by a necrotizing granulomatous inflammation of the arterioles and venules. Other vasculitides include: systemic lupus erythematosus and polyarteritis nodosa. Kimura's disease occurs most commonly in Asians, and it is characterized by vascular proliferation, lymphoid hyperplasia, and eosinophilic inflammation. Less commonly seen non-infectious inflammations include: necrobiotic xanthogranuloma with paraproteinemia, pseudorheumatoid nodules, foreign body granulomas, histiocytosis X, sinus histiocytosis, juvenile xanthogranuloma, and Erdheim–Chester disease.

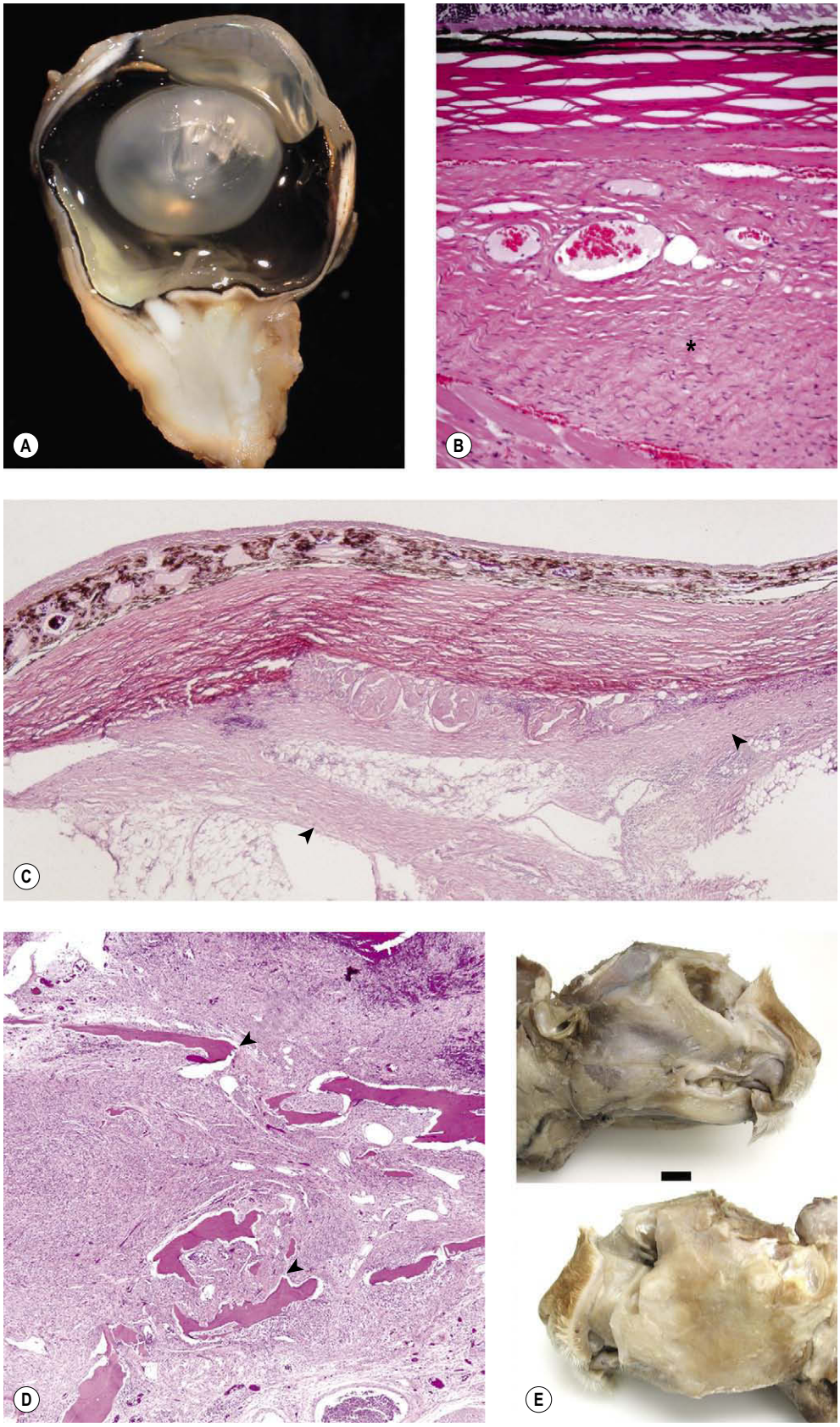


Figure 6.6 Feline restrictive orbital sarcoma (orbital sclerosing pseudotumor). (A) Gross photograph of feline globe and orbital tissues showing orbital contents bound together by bland neoplastic fibrous tissue in restrictive orbital sarcoma. (B) Photomicrograph showing sclera and spindle-cell proliferative reaction in the episcleral orbital tissue (*). (C) Low magnification photomicrograph showing fibrous tissue (arrows) wrapped around the sclera, adipose tissue and facial planes. (D) Photomicrograph showing the orbit from a cat eventually euthanized with feline restrictive orbital sarcoma showing neoplastic tissue associated with bone lysis (arrows). (E) Gross photograph of the head of the cat euthanized with feline restrictive orbital sarcoma. The upper image shows the side of the head not affected with neoplastic tissue and the lower image is of the side of the head affected. The affected side shows a blanket of neoplastic tissue covering the facial planes and obscuring muscles. Notice that there is no well-defined mass lesion, even in this late stage of disease.

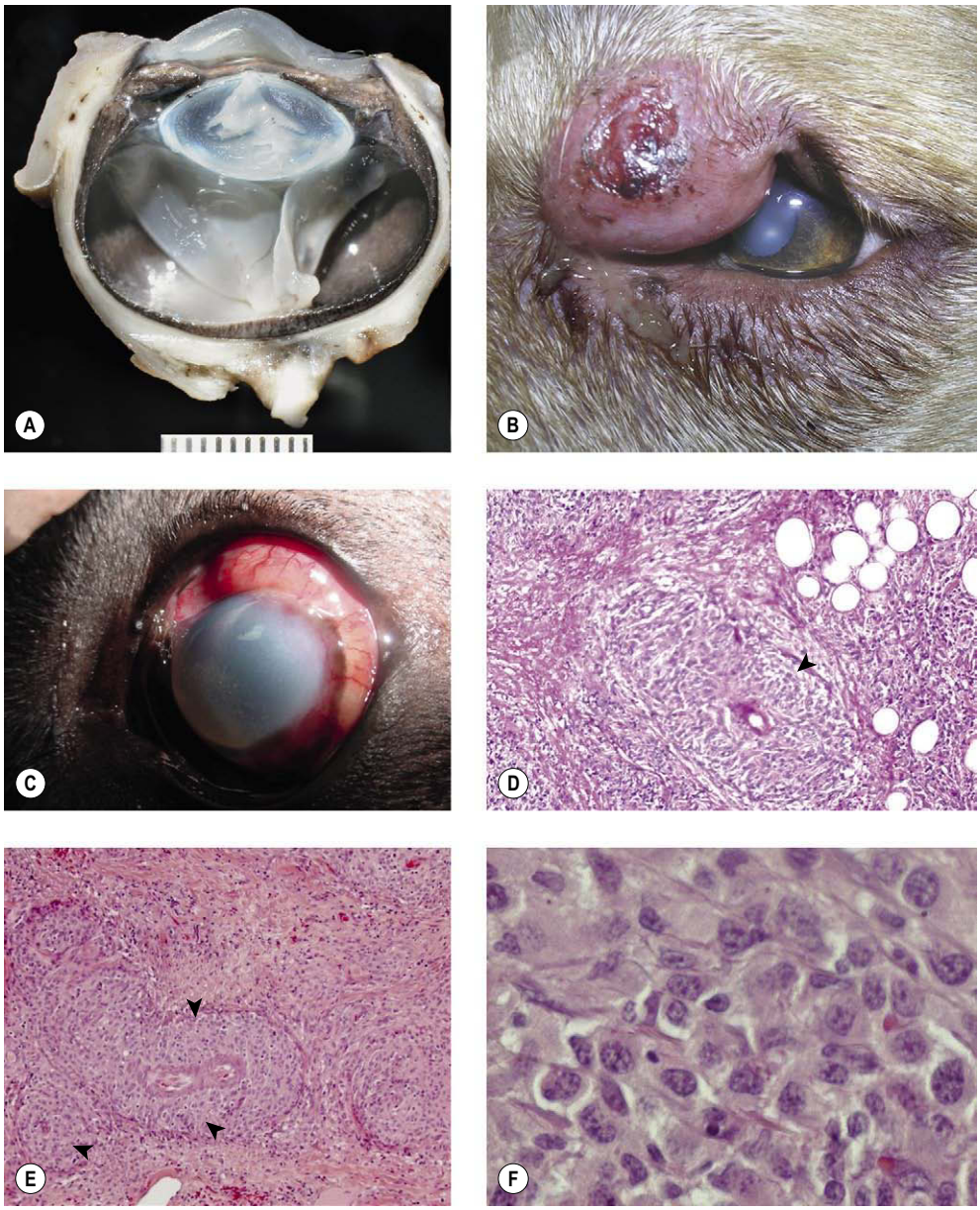


Figure 6.7 Canine systemic histiocytosis. (A) Gross photograph of a globe with systemic histiocytosis, causing a diffuse swelling in the uveal tissues. (B) Clinical photograph showing an eyelid nodule with systemic histiocytosis. (Image courtesy of Jane Cho.) (C) Clinical photograph showing episcleral tissue swelling associated with systemic histiocytosis. (D,E) Photomicrographs of systemic histiocytosis showing vasocentric histiocytic infiltrate (arrows). (F) Higher magnification photomicrograph showing atypical histiocytic cells, which predominate in systemic histiocytosis.

CYSTIC LESIONS OF THE ORBIT

Acquired conjunctival cyst (Fig. 6.8)

There are 13 cases of acquired cysts diagnosed in the COPLOW collection.

- Acquired cysts are the result of the traumatic displacement of epithelial tissue which then develops into a cystic lesion is the displaced location
  - Acquired cysts can develop after trauma or surgery
  - Most cases occurred as a complication following enucleation surgery
- Conjunctival cyst is characterized by the following features:
  - Fully-differentiated conjunctival epithelium or stratified squamous epithelium surrounded by a fibrous capsule
  - Inflammation may or may not be a feature
  - Some cases have excessive keratinization within the cyst.

Dermoid cyst

- These are rare congenital cystic lesions that may occur within the orbit. Although isolated canine and equine cases are reported in the veterinary literature, this diagnosis is not represented in the COPLOW archive
- These lesions are present at early age, probably from birth, but may not present clinically until adulthood due to slowly progressive enlargement of the cyst
- Morphologic features of dermoid cyst include:
  - Contain fully-differentiated but disorganized epidermal structures such as stratified squamous epithelium, hair follicles, sebaceous glands or sweat glands
  - Rarely they contain other structures of surface ectodermal origin.









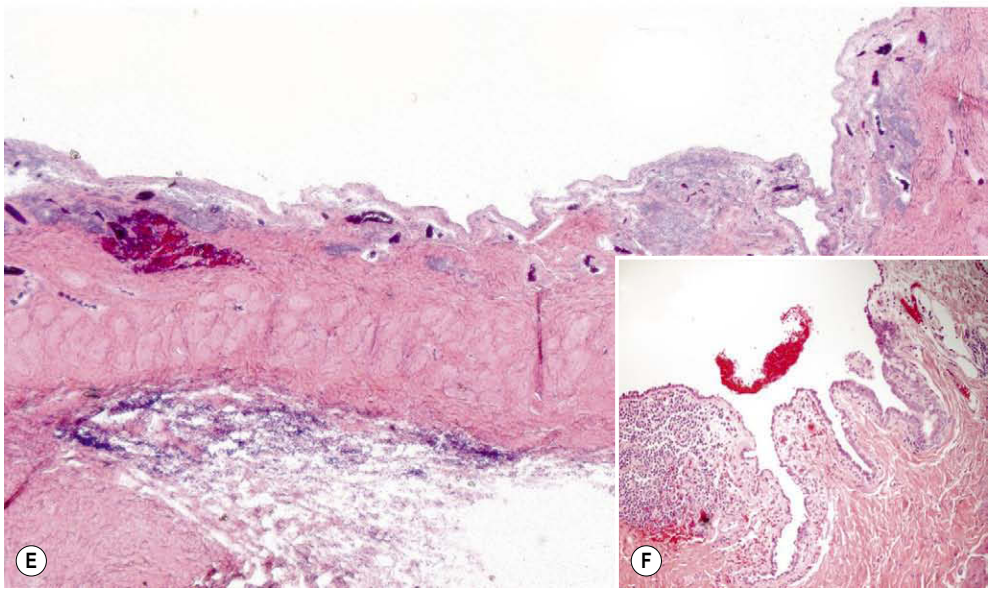


Figure 6.8 Conjunctival epithelial cysts of the orbit. (A) DSH, 7 years old: the right globe was enucleated 3 months previously. A soft swelling was present within the bony orbit at the arrow. (B) Gross photograph of the cyst dissected from the orbit of (A). (C) Golden Retriever, 2 years old: the dark area below the globe represents a large inferior subpalpebral cyst. (D) This brown serous fluid is from the fine needle aspirate of the cyst shown in (C). (E,F) Photomicrographs showing the inner epithelium and the fibrous wall of conjunctival cysts in dogs.



Figure 6.9 Mucocele of the lacrimal glands of the nictitans. (A) English bulldog, 9 months old: bilateral hypertrophy glands nictitans were surgically treated with the pocket technique 3 months before the photograph. (B) This photograph of the left eye of (A) shows the large cystic structure protruding from the bulbar surface of the nictitans. The arrow points to the normal free lid margin of the nictitans. (C) Photomicrograph showing the cyst epithelium, which is cuboidal epithelium and the loose connective tissue immediately outside the cyst.

Salivary or lacrimal ductular cyst (Fig. 6.9)

There are eight cases of orbital salivary ductular cysts in the COPLOW collection.

- These cysts can be associated with the lacrimal gland or the zygomatic salivary gland
- Morphologic features characteristic of ductular cyst
  - In order to make the diagnosis of ductular cyst, there has to be an epithelial lining to the inner aspect of the cyst
  - The cyst wall may be thin and fibrous and devoid of inflammation. However, the adjacent associated glandular tissue often demonstrates an inflammatory infiltrate and fibrosis
  - There may or may not be evidence of a mucinous component within the cyst.

Zygomatic salivary mucocele (Fig. 6.10)

There are six cases diagnosed in the COPLOW collection.

- Morphologic features helpful in making the diagnosis of mucocele include:
  - Mucocele has a thick fibrous capsule but no epithelium. For that reason, mucocele is not a truly cystic lesion
  - PAS + mucin is an important component within the cavitated lesion and also within the connective tissues around the cavitated lesion
    - The 'mucoid' appearance of the connective tissues may lead to the misdiagnosis of myxosarcoma
  - Away from the cavitary lesion containing thick, mucinous material, there is granulation tissue, inflammation, or evidence of recent or old hemorrhage
  - It is unclear whether the inflammatory changes or hemorrhage described above are indicative of trauma related to attempts to obtain aspirates from the lesion, or tissue response to the liberation of salivary secretion, or whether they support an underlying inflammatory process (sialadenitis)
    - Sialadenitis may be an important consideration in the etiopathogenesis of zygomatic salivary mucoceles, given that some cases appear to resolve with conservative management including anti-inflammatory and antibiotic therapy.

Comparative Comments

Regarding cystic lesions of the orbit, congenital epithelial cysts are common. These are subgrouped into epidermoid, dermoid, conjunctival dermoid, and cysts lined by other types of epithelium. Acquired epithelial cysts include: mucocele, caused by erosion or displacement of sinus epithelium into the orbit; lacrimal ductal cysts; and implantation cysts. Neurogenic cysts may arise as a result of

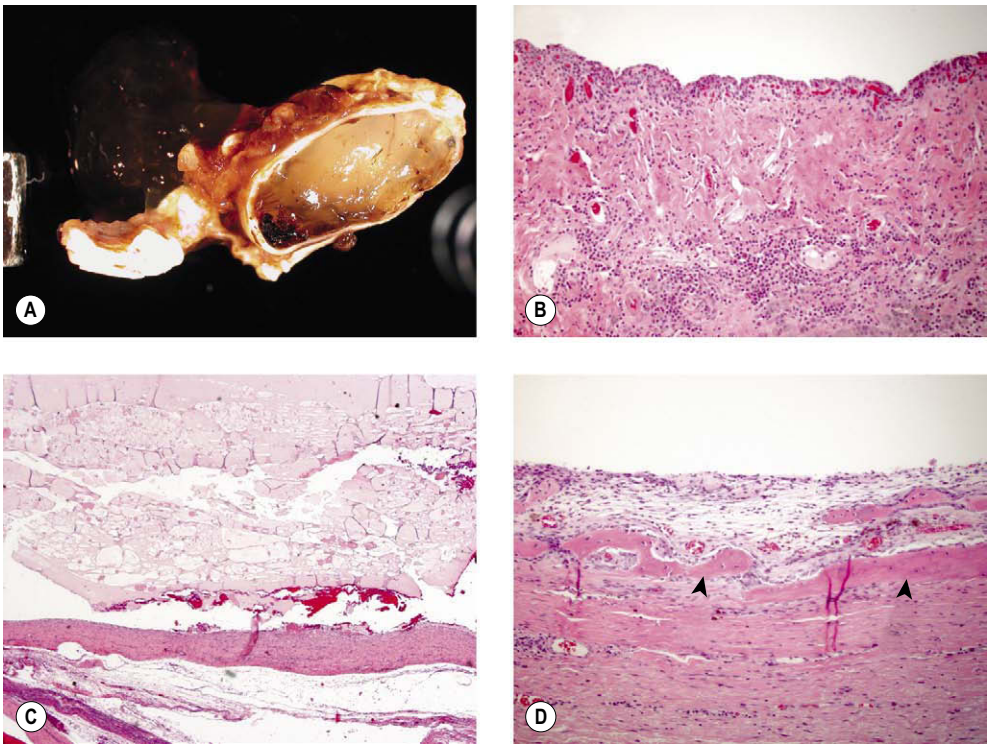


Figure 6.10 Orbital salivary mucocele. (A) Gross photograph of an orbital mucocele removed at orbitotomy. (B–D) Photomicrographs of orbital mucocele showing a mesenchymal pseudoepithelium and a thick fibrous capsule. (D) Osseous metaplasia (arrows).

Comparative Comments (continued)

developmental abnormalities of the eyes and are lined by neuroepithelia. Hematic cysts result from repeated hemorrhage into softer bony tissue in the orbit, in association with lymphangioma or other pre-existing lesions.

VASCULAR LESIONS OF THE ORBIT

There are two cases of orbital arteriovenous or venous malformations in the COPLOW collection.

- Rarely, congenital or acquired arteriovenous fistulae or orbital varices may present with exophthalmos
- Exophthalmos associated with vascular lesions may be intermittent and/or pulsatile.

ORBITAL FAT PROLAPSE (HERNIATION) (Fig. 6.11)

- There are four canine cases of this condition diagnosed in the COPLOW collection.
  - The condition has also been reported in other species, including horses
- The diagnosis is made by recognizing a mass of fully differentiated adipose tissue and ruling out other conditions
  - This can be difficult to distinguish pathologically from lipoma, and clinical features, including presence of a distinct mass lesion within the orbit, detected on ultrasonography, may suggest a diagnosis of lipoma rather than prolapse of normal adipose tissue.

Comparative Comments

Not uncommonly, orbital fat will prolapse through the orbital septum in humans and cause a 'lump' in the lids. This may be removed for diagnostic purposes or as a cosmetic procedure.

NEOPLASTIC DISEASES

Lymphoma (Figs 6.12, 6.13)

There are 12 canine cases of orbital lymphoma in the COPLOW collection, representing 0.3% of canine neoplasms and 7% of canine lymphomas in the collection. There are 11 feline cases of orbital lymphoma in the COPLOW collection, representing 0.5% of feline neoplasms and 5% of feline lymphomas in the collection.

- Orbital lymphoma is most common in the bovine dairy breeds, but this is not well represented in the COPLOW case material due to the predominance of companion animal submissions
- There are three cases of orbital lymphoma in ferrets in the COPLOW collection, out of a total of 11 ferret submissions
- Lymphoma should always be considered a systemic disease unless there is a compelling reason to believe that a particular organ is primarily involved (see Ch. 5). Lymphoma involving the orbit should be considered part of a systemic process.

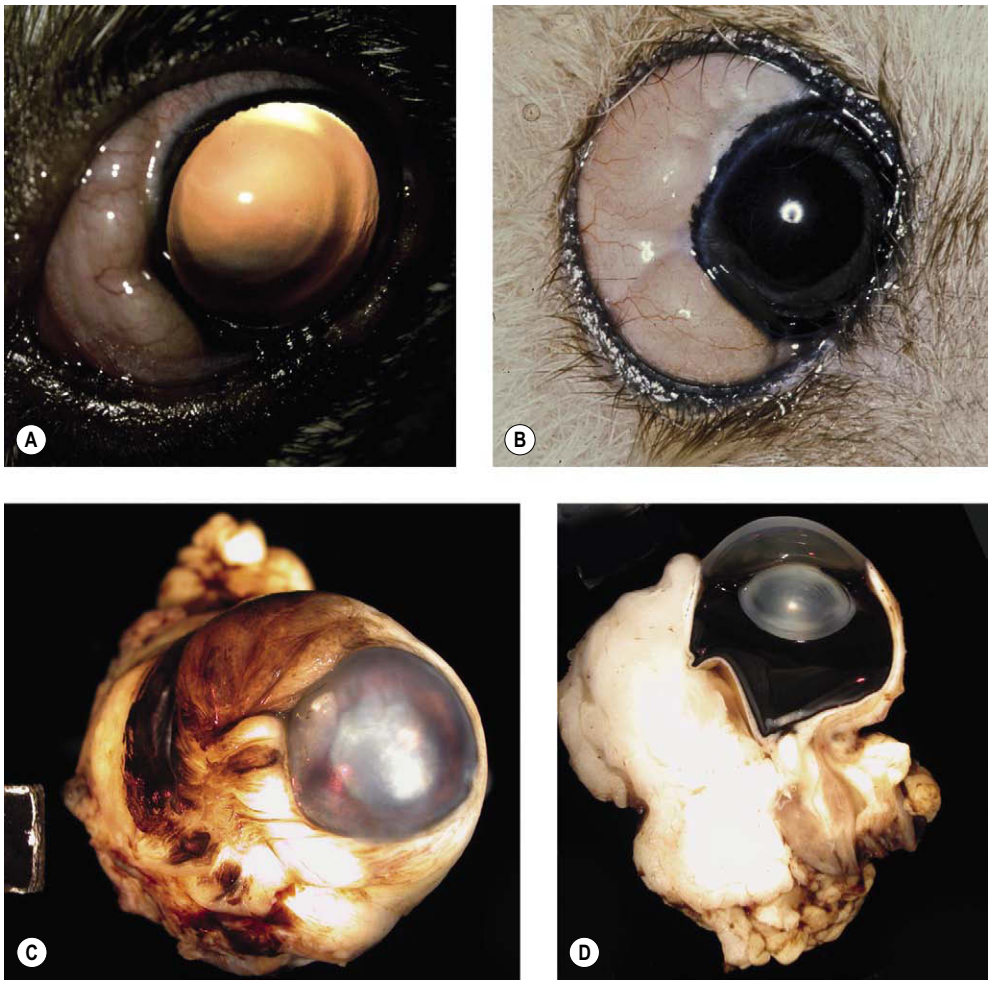


Figure 6.11 Orbital fat prolapse (lipoma). (A) Beagle, 10 years old: lobulated subconjunctival masses are present at the nasal bulbar conjunctiva. Fine needle aspirate (FNA) confirmed fully-differentiated adipose tissue. (B) Opossum, adult: this is the right eye of a grossly overweight pet. A FNA confirmed normal adipose tissue in these subconjunctival masses. (C,D) Gross photographs showing orbital adipose tissue prolapsed forward, distorting the conjunctival profile.

Soft tissue sarcomas (Fig. 6.14)

Fibrosarcoma, high grade

There are eight canine cases and two feline cases in the COPLOW collection.

- The morphologic features useful in reaching a diagnosis of high-grade fibrosarcoma are as follows:
  - Spindle-shaped cellular profile
  - Extracellular collagen deposition
- These tumors should be graded in order to offer the most accurate prognosis, although our impression is that the orbit is an unfavorable location for a soft tissue sarcoma of any kind. The grading system of Barbara Powers is used by COPLOW and described below:
  - Feature 1: Cellular differentiation, scored from 1 (tumor cells resemble normal tissue cells) to 3 (tumor cells are very anaplastic)
  - Feature 2: Mitotic rate, expressed as number of mitotic figures per ten ×400 microscopic fields
    - 1 = 1 to 9
    - 2 = 10 to 19
    - 3 = More than 20
  - Feature 3: Tumor necrosis
    - 1 = No necrosis
    - 2 = Less than 50% of the tissue is necrotic
    - 3 = More than 50% of the tissue is necrotic
  - Total scores of 3 or 4 are grade 1 sarcomas, scores of 5 or 6 are grade 2 sarcomas, and scores of 7 to 9 are grade 3 sarcomas.

Morphologically low-grade, biologically high-grade fibrosarcoma of dogs (Fig. 6.15)

There are six cases of this tumor in the COPLOW collection, representing 0.15% of canine tumors in the collection.

- As the awkward name suggests, this tumor of the soft tissues of the canine skull defies the sarcoma grading scheme described above and needs to be carefully evaluated in order to make an accurate diagnosis
- These tumors have a breed predilection for the Golden Retriever, but can affect any breed of dog
- These are locally aggressive tumors of the skull and they carry a poor prognosis
- In order to accurately diagnose these challenging neoplasms, the following morphologic features must be taken into consideration:
  - The hallmark feature of the morphologically low-grade, biologically high-grade sarcoma is abundant collagen within the neoplastic tissue
  - By grading criteria, this is a grade 1 (low-grade) sarcoma for the following reasons:

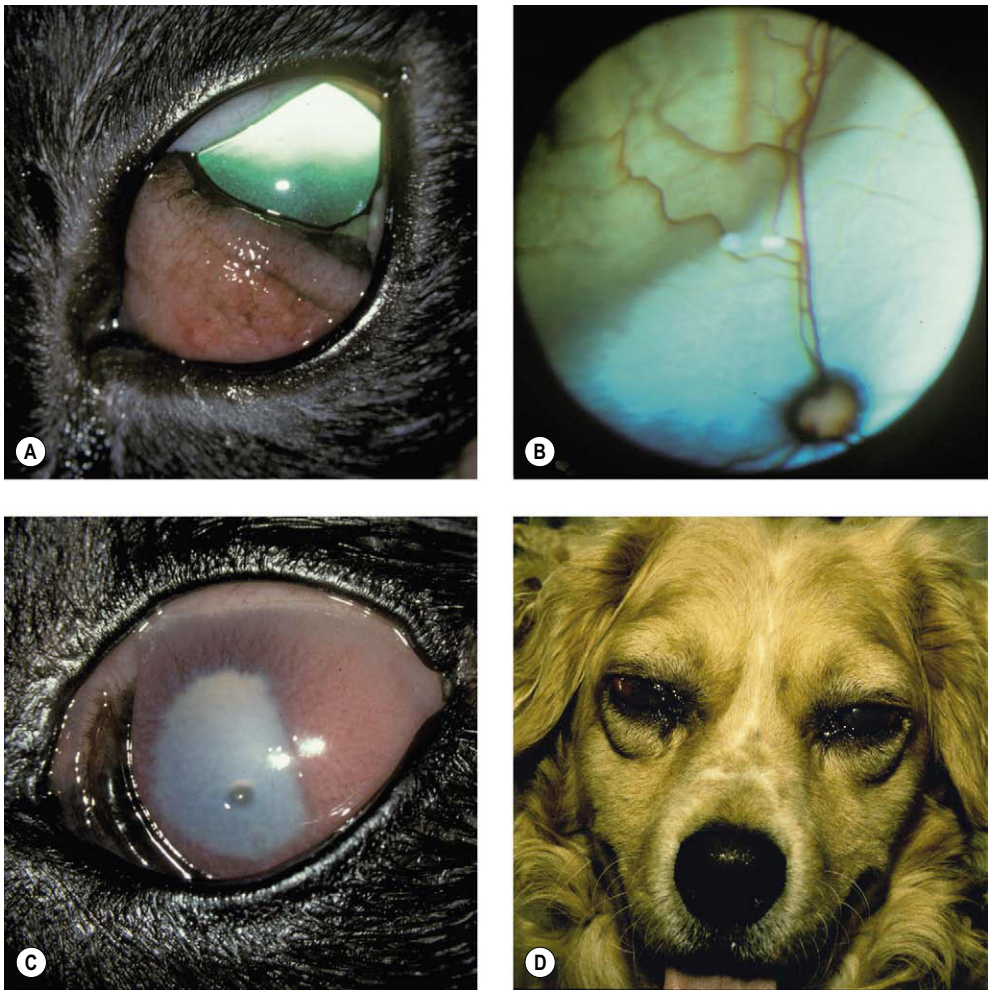


Figure 6.12 Orbital lymphoma, clinical. (A) DSH, 1 year old: the globe is exophthalmic and the nictitans is prolapsed. (B) The fundus of the eye in (A) shows a change in the tapetal coloration superior and nasal due to indentation of the globe by a retrobulbar mass. The mass was identified by FNA as lymphoma. (C) Border Collie, 10 years old: severe corneal edema and vascularization prevents visualization of the anterior segment in this exophthalmic globe. Retrobulbar and intraocular lymphoma was diagnosed at necropsy. (D) Golden Retriever mix, 5 years old: both globes are exophthalmic with swelling of upper and lower lids. Retrobulbar and intraocular lymphoma was diagnosed by FNA and confirmed at necropsy.

  - The neoplastic cells either look exactly like native fibroblasts, or they have only mild cellular enlargement and large nuclei
  - Mitoses and necrosis are never prominent in these tumors
- The challenge for the pathologist is to accurately distinguish between sarcoma and granulation tissue. The following features are helpful:
  - Granulation tissue has a prominent vascular bed, with small blood vessels crossing at right angles to the direction of the spindle cells and collagen fibers; whereas sarcoma has fewer vessels and a more random distribution of blood vessels
- The challenge for the pathologist lies in answering the question of whether or not the lesion is neoplastic or reactive
  - However, the clinician might already consider the lesion as being neoplastic, because of its aggressive and extensive behavior
  - In these cases, it can be rewarding for pathologist to seek further input from the submitting clinician regarding their impression of the lesion's biological behavior
- If the clinician is reluctant to determine that the lesion is neoplastic, particularly if it is early in the course of the disease, then the pathologist is faced with a difficult diagnostic decision.

Anaplastic sarcoma (Fig. 6.16)

There are 10 cases of this orbital tumor in dogs and three cases of this tumor in cats in the COPLOW collection.

- These are, by definition, high-grade sarcomas, due to their lack of the features of tissue differentiation and failure to form any extracellular matrix, by which a more specific name can be given.

Liposarcoma (Fig. 6.17)

There are 10 cases of orbital liposarcomas in the COPLOW collection, all of them in dogs.

- There are two morphologic subtypes:
  - Anaplastic tumors showing the following features:
    - Cellular pleomorphism
    - Multinucleate cells
    - Scant extracellular matrix
    - Lipid vacuoles in the cytoplasm
  - Sharply delineated nodular masses with features of brown fat (hibernoma) showing the following features:
    - Delineated nodules with little focal invasion
    - Large monomorphic neoplastic cells with abundant delicately vacuolated cytoplasm
    - A rich capillary vascular supply.

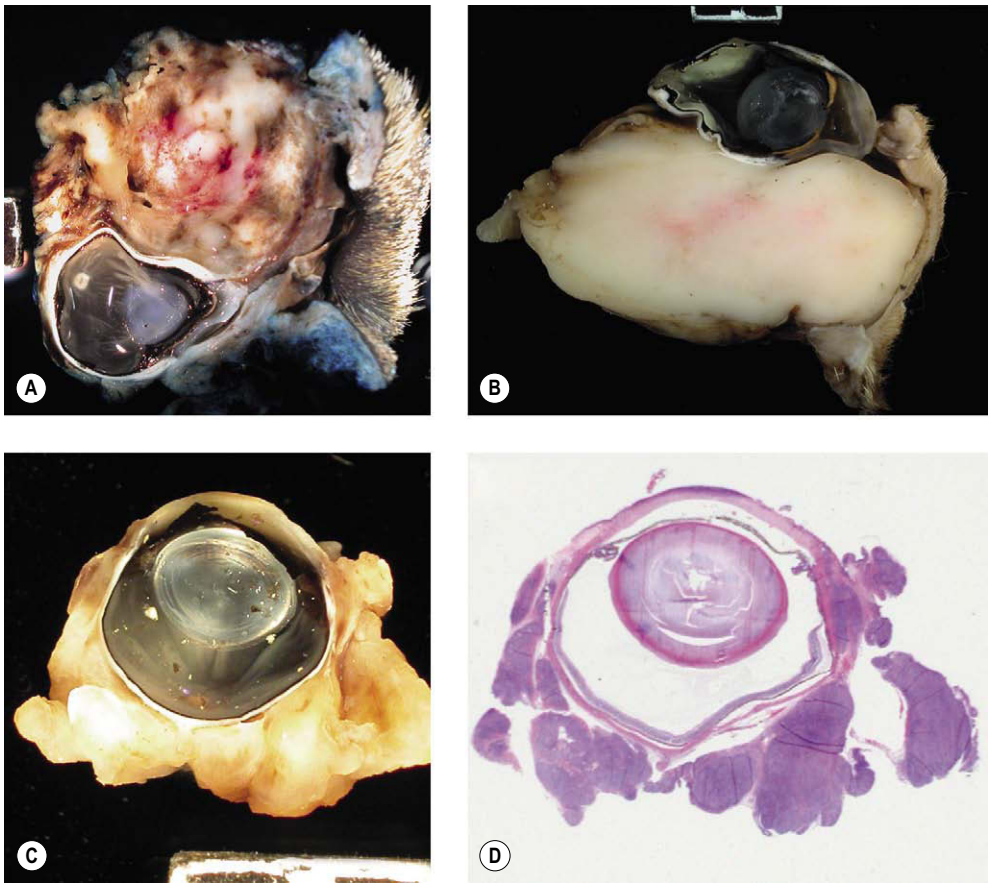


Figure 6.13 Orbital lymphoma, pathology. (A,B) Gross photographs of canine globes with orbital lymphoma. (C,D) Gross photograph and subgross photomicrograph of a ferret globe with orbital lymphoma.

Extraskeletal osteosarcoma (Fig. 6.18)

There are seven cases of extraskeletal osteosarcoma of the orbit in dogs and four cases in cats in the COPLOW collection.

- The defining feature is the extracellular deposition of osteoid matrix in tumors that do not arise from bone
- Orbital osteosarcomas may or may not be directly connected to the orbital bone
- One case in a cat arose within the fibrous reaction surrounding an orbital prosthesis implanted after enucleation years before.

Rhabdomyosarcoma (Fig. 6.19)

There are seven cases of orbital rhabdomyosarcoma in dogs in the COPLOW collection.

- Morphologic features of diagnostic significance include the following:
  - Strap cells with abundant cytoplasm, parallel cell boundaries, and multiple lined up nuclei
  - Cross striations in the cytoplasm
  - Positive desmin, actin, myoglobin, or skeletal muscle actin labeling by immunohistochemistry
- Five of the seven cases are in dogs less than 3 years old.

Hemangiosarcoma

There are six cases of orbital hemangiosarcoma in dogs and three cases in cats in the COPLOW collection.

- These tumors can be either primary or secondary, but there are no reliable morphologic features to make a distinction
- Morphologic features of diagnostic importance are as follows:
  - The morphologic hallmark of the tumor is the relationship between neoplastic cells and the red blood cells around them. In hemangiosarcoma the RBCs are within slit-like spaces defined by the tumor cells.
  - The cellular profile can be extremely variable, ranging from primarily spindle cells, to polygonal cells with an epithelial appearance, to anaplastic forms.

Tumors of the skull, extending to the orbit

Osteosarcoma (Fig. 6.20)

There are 10 cases of orbital osteosarcoma in dogs and three cases in cats in the COPLOW collection.

- In dogs, osteosarcoma of the axial skeleton, including the skull, is rarer than osteosarcoma of the appendicular skeleton, and less likely to spread by systemic metastasis. However, this distinction in biological behavior may be of limited clinical and prognostic significance because radical surgical excision by amputation is not an option
- Generally, osteosarcoma of the skull in dogs grows outwards from the skull
- The histological appearance can be that of a well-differentiated tumor suggesting a low-grade neoplasm in terms of biological

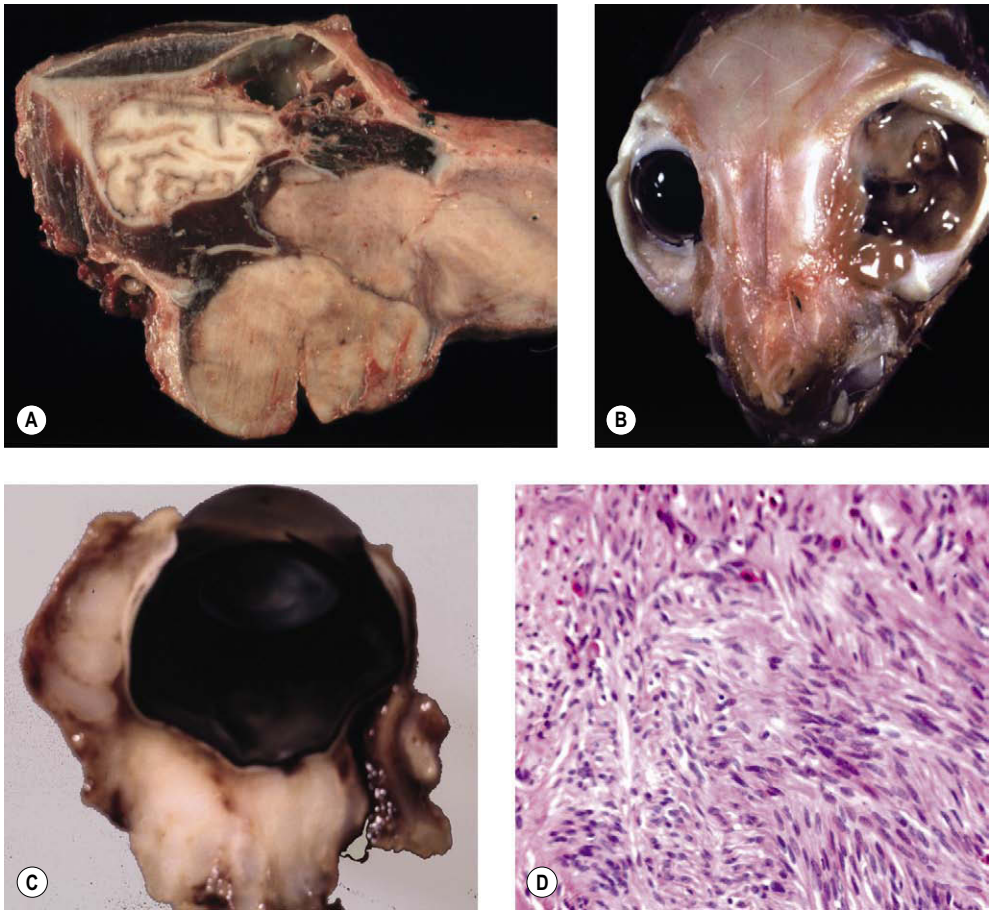


Figure 6.14 Orbital fibrosarcoma. (A) Gross photograph of a canine skull sectioned in the midline. A very large invasive fibrosarcoma is destroying much of the hard palate as well as the orbit. (B) Gross photograph of a feline skull with the recurrent orbital fibrosarcoma apparent in the exposed orbital tissue. (C) Gross photograph of a canine globe with orbital fibrosarcoma. (D) Photomicrograph of orbital fibrosarcoma.

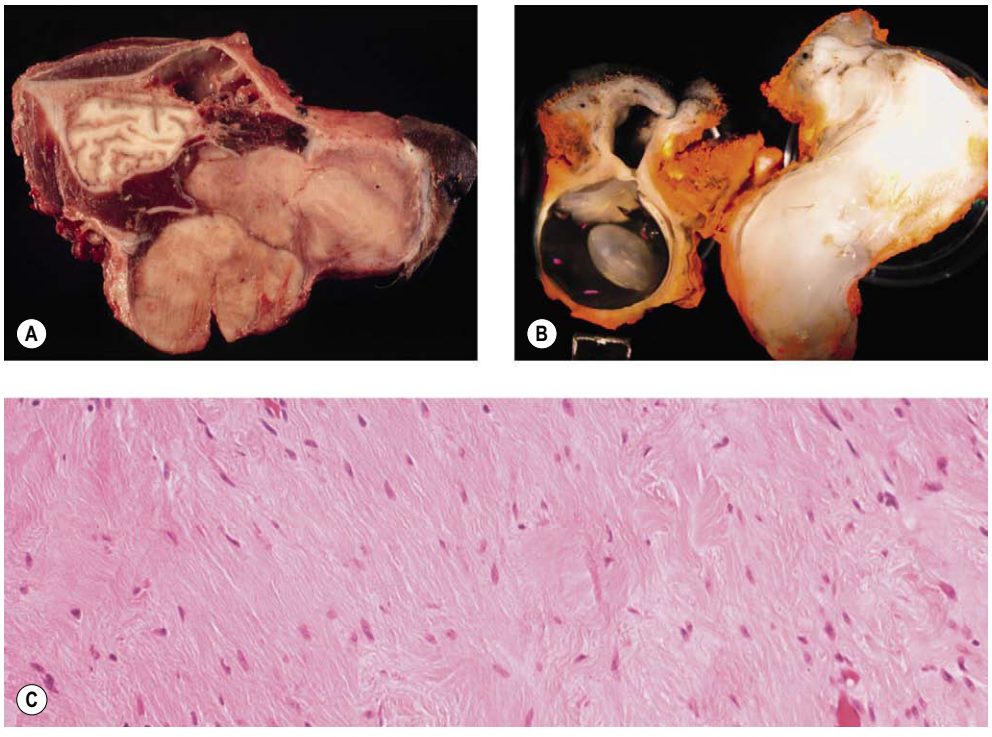


Figure 6.15 Morphologically low-grade, biologically high-grade fibrosarcoma. (A) Canine skull with an extensive morphologically low-grade, biologically high-grade fibrosarcoma. Sarcoma has effaced much of the maxilla. (B) Gross photograph of globe and orbital tissues from a dog with morphologically low-grade, biologically high-grade fibrosarcoma. (C) Photomicrograph showing bland collagen-rich connective tissues and sparse well-differentiated fibroblasts.

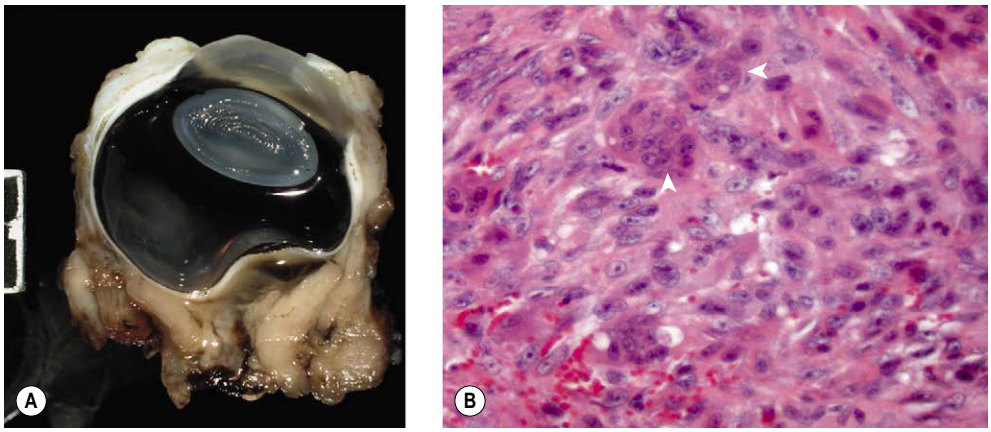


Figure 6.16 Orbital anaplastic sarcoma. (A) Gross photograph of canine globe and orbital anaplastic sarcoma. (B) Photomicrograph of orbital anaplastic sarcoma showing poorly-differentiated neoplastic cells, including multinucleate giant cells (arrows).

behavior. However, aside from radical orbitectomy, which is a technically demanding procedure, there are few good surgical options. Radical excision, combined with adjunctive therapy may be of benefit in some patients.

Canine multilobular tumor of bone (chondroma rodens) (Fig. 6.21)

There are 12 cases of canine multilobular tumor of bone in the COPLOW collection.

- These are always tumors of the skull and often arise in suture lines between the flat bones of the skull
- They are locally effacing and aggressive, but they only rarely metastasize. Thus, local recurrence following excision is a problem but relatively long survival times may be achieved
- Morphologic features useful in establishing a diagnosis are as follows:
  - As the name suggests, these tumors have a very characteristic lobulated pattern
    - Each lobule is always surrounded by collagen rich spindle cells and not bone or cartilage matrix
    - Within the nodule (or lobule), there is fully differentiated bone, cartilage, or both, with accompanying osteocytes and chondrocytes.

Feline skeletal osteochondromatosis (multiple cartilaginous exostoses) (Fig. 6.22)

- Affected cats develop one, or several, widely separated boney proliferations that grow outward from the skeleton, distorting the surrounding soft tissue
  - Multifocal osteochondromatosis can occur in any bone as exostotic skeletal masses, and often involve the skull and orbit
- Unlike osteochondromatosis in young dogs, which occurs near growth plates and stops growing when the growth plate closes, the feline tumors continue to grow relentlessly after skeletal maturity. They therefore carry a much poorer prognosis
- Tumors often affect the skull and/or less frequently the long bones
- Tumors are made up of a mixture of well-differentiated bone and cartilage, often, but not always, with features that resemble a growth plate in the relationship between bone and cartilage
- If incompletely excised, tumors can grow back with more malignant features
- A possible association with retroviral infection has been proposed but the causal relationship between naturally occurring FeLV infection and this form of hyperostosis remains unconvincing.

Other hyperostotic syndromes that may affect the orbit

- Craniomandibular osteopathy is characterized by irregular osseous proliferation of the skull bones in young dogs. Scottish, Cairn and West Highland white terriers are predisposed to this condition, that may affect orbital structures, leading to exophthalmos
- Idiopathic calvarial hyperostosis has been reported in young male Bull mastiffs. This rare syndrome of excessive bone proliferation affecting the calvarium may involve bones of the orbit, producing a mass effect or impinging on neurovascular structures
- Both of these conditions appear to be self-limiting when affected animals reach skeletal maturity.

Canine orbital meningioma (Figs 6.23, 6.24)

There are 60 cases of canine orbital meningioma in the COPLOW collection, representing 1.5% of canine tumors in the collection.

- This tumor shows distinctive morphology and biological behavior in the dog
- Characteristically, orbital meningiomas envelope the optic nerve outside the dura mater invading adipose tissue and loose connective tissues. Tumors form a cone around the optic nerve that conforms to the shape of the orbit
- Neoplastic cells are derived from the arachnoid cap cells which normally exist outside the dura mater near the globe, as discussed in Chapter 12
  - Tumor cells may or may not extend into the dura mater, but they are always outside the dura because of the extradural origin
- These tumors are slow growing but hard to excise completely. Thus, local recurrence is relatively common. They can locally infiltrate into the optic foramen, and cranial vault and may displace or invade the brain, optic chiasm and contralateral

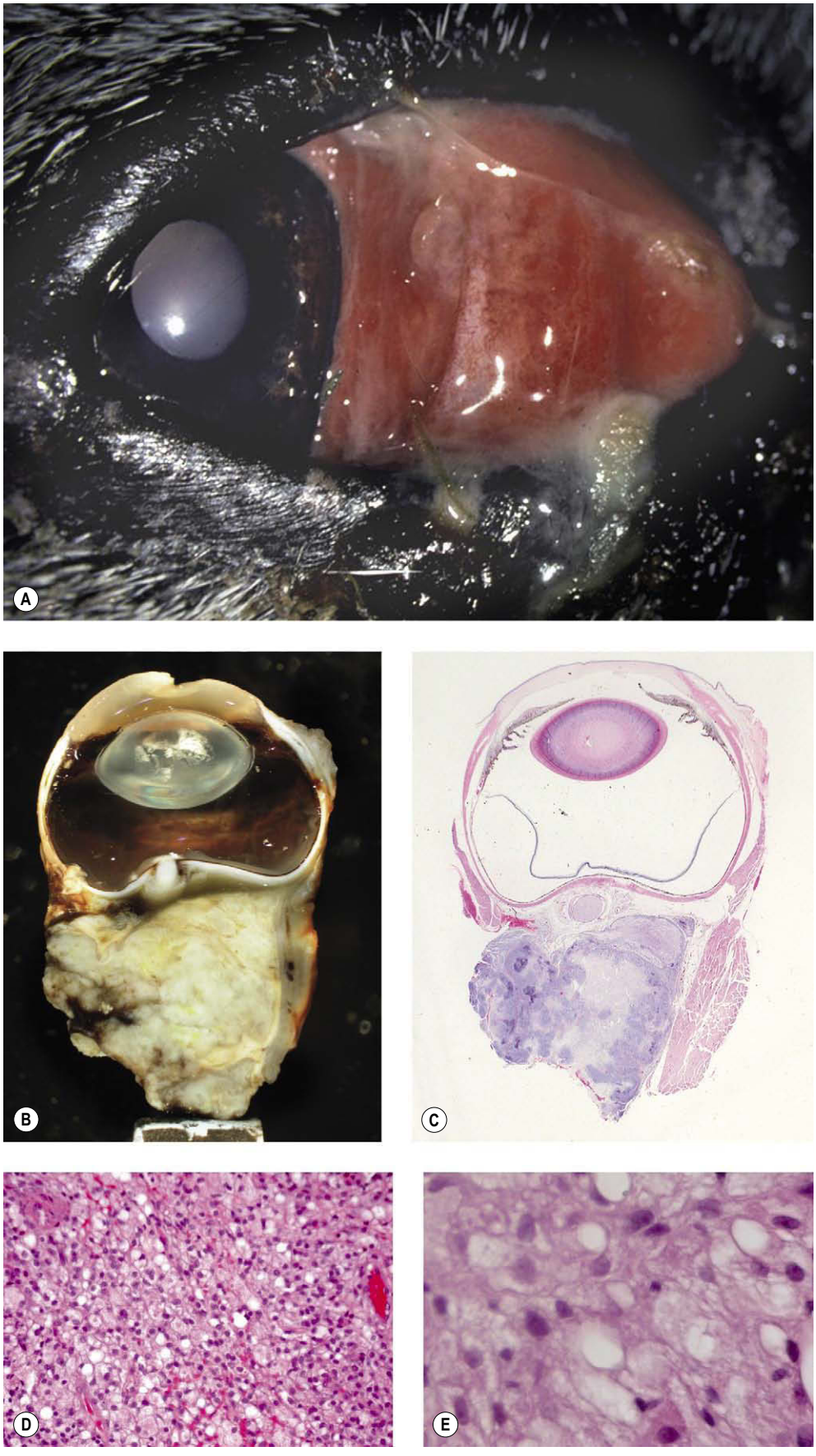
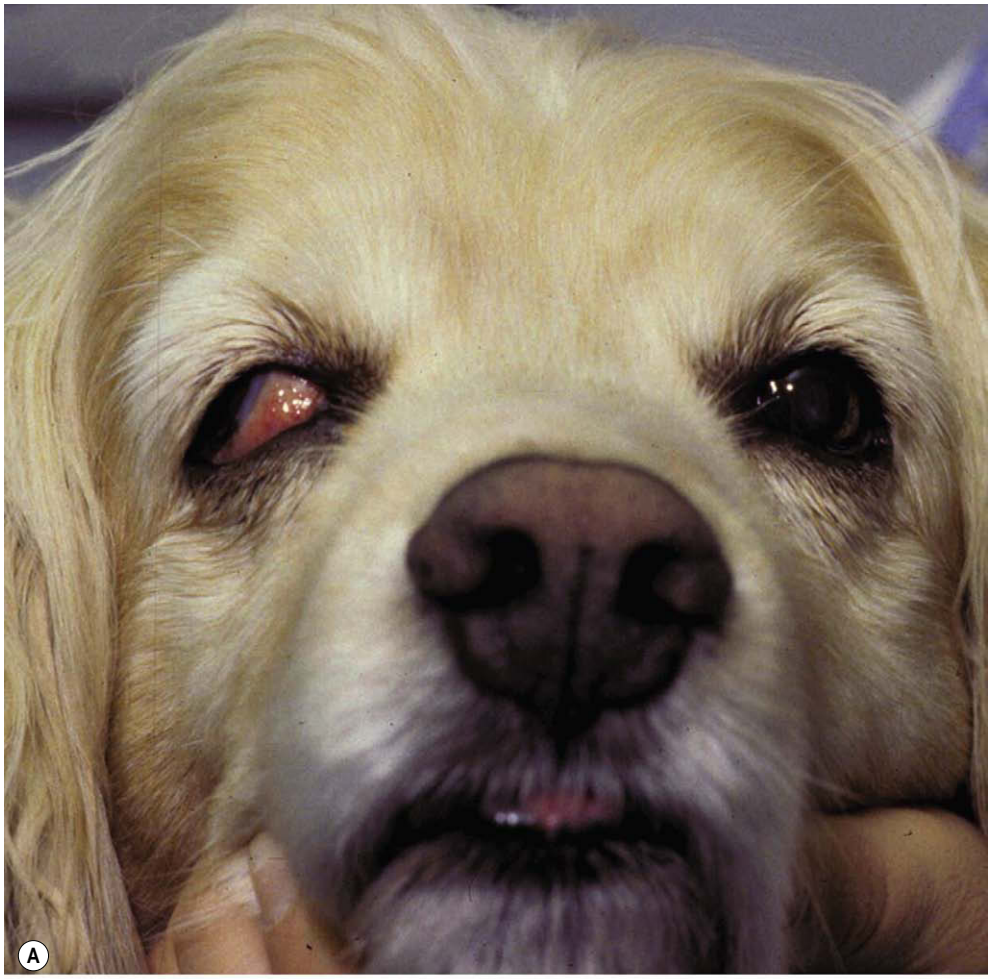


Figure 6.17 Orbital liposarcoma. (A) Boxer, 10 years old: the large mass caused an exophthalmic and temporal-deviated globe. The neoplasia extended into the base of the third eyelid. (B,C) Gross photograph and subgross photomicrograph showing liposarcoma in the orbit. (D,E) Photomicrographs showing neoplastic adipocytes with characteristic vacuolated cytoplasm.





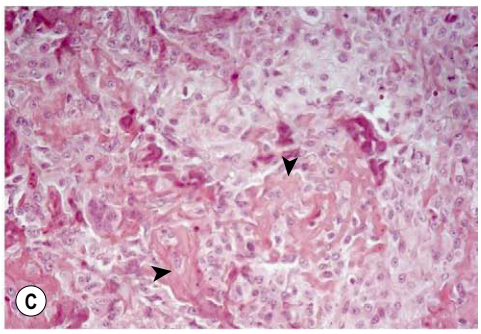
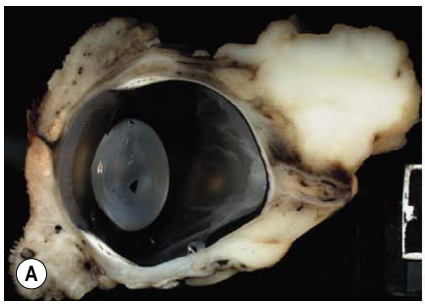


Figure 6.18 Orbital extraskeletal osteosarcoma. (A) Cocker Spaniel, 10 years old: the third eyelid is prolapsed. The extensive tumor was diagnosed by FNA. The mass contributed to the swelling in the temporal area. (B) Gross photograph of orbital extraskeletal osteosarcoma involving the soft tissues of the orbit. (C) Photomicrograph of orbital extraskeletal osteosarcoma showing neoplastic osteoid deposition (arrows).



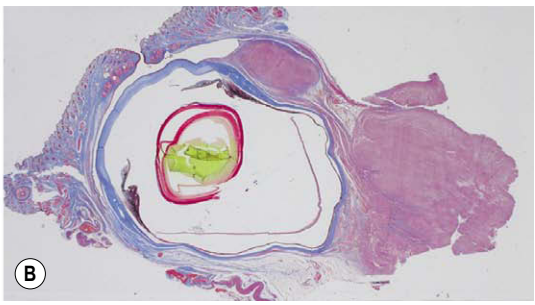


Figure 6.19 Orbital rhabdomyosarcoma. (A,B) Gross photograph and subgross photomicrograph of orbital rhabdomyosarcoma.

optic nerve. Metastasis is uncommon, but has been reported in isolated cases

- Morphologic features useful in the diagnosis of canine orbital meningioma include:
  - Tumors are solid near the optic nerve and show invasion between individual adipocytes, loose connective tissue, or myocytes away from the optic nerve
  - The most common cellular profile of the neoplastic cells is meningotheliomatous, with a very epithelial-like appearance
    - Neoplastic cells have abundant cytoplasm, polygonal shape, and form tight aggregates, all of which makes them appear as epithelial cells
    - This tumor is often misdiagnosed as squamous cell carcinoma by the uninitiated pathologist
    - When in doubt, canine orbital meningioma is generally vimentin-positive and cytokeratin negative on immunohistochemistry
  - Less commonly, the neoplastic cells will be spindle cells with characteristic cellular whorls, more familiar as features of meningioma to pathologists with more experience diagnosing intracranial meningiomas
  - A very characteristic feature present in about 90% of canine orbital meningiomas, but never seen in intracranial meningioma, is the presence of foci of myxomatous, cartilaginous, or osseous metaplasia
    - This can be a useful diagnostic feature if detected on diagnostic imaging.

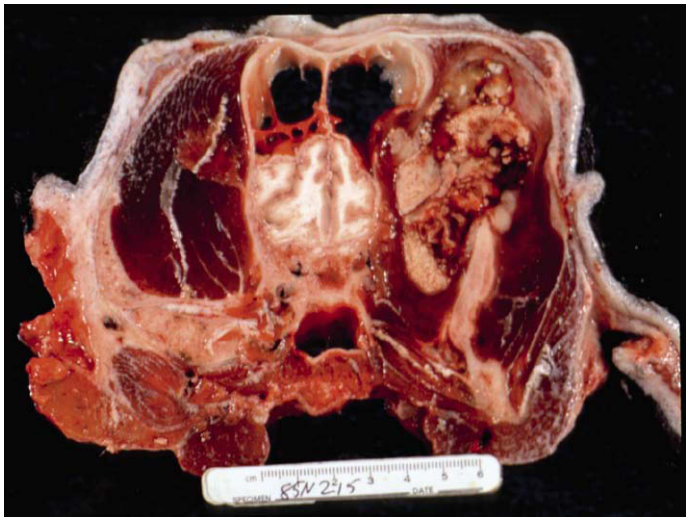


Figure 6.20 Osteosarcoma of the skull. Gross photograph of a sectioned canine skull showing orbital osteosarcoma extending from the bony orbit.

Salivary or lacrimal gland adenocarcinomas (Fig. 6.25)

There are seven cases in dogs and two cases in cats within the COPLOW collection of solitary tumors arising from the zygomatic salivary gland or the lacrimal gland.

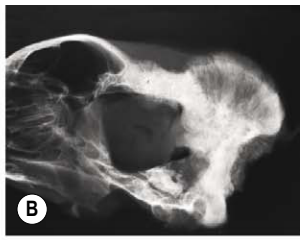
- Often their location within the orbit was considered to provide clues as to the likely tissue of origin, e.g. within the superior orbit is likely to be lacrimal in origin, rather than zygomatic salivary gland tumors which arise in the inferior orbit
- Adenocarcinoma of the gland of the third eyelid may also extend posteriorly into the orbit leading to exophthalmos
- The majority of salivary gland tumors are malignant but little is known about tumors of the lacrimal gland or zygomatic salivary gland specifically.

Canine orbital multilobular adenoma (Fig. 6.26)

There are 29 cases of canine orbital multilobular adenoma in the COPLOW collection, representing 0.65% of the total number of canine tumors in the collection.

- These tumors may present as either conjunctival swellings or as space-occupying orbital mass lesions
- The appearance at surgery is quite distinctive and the following are characteristic features:
  - The lesions consist of soft, translucent lobules, each with a thin capsule, that are tenuously connected together. This feature makes them very hard to grasp and dissect. Because of this, excision is seldom complete unless enucleation or exenteration are performed
  - Although benign, tumors often recur within 1–2 years of excision, and rare cases are bilateral





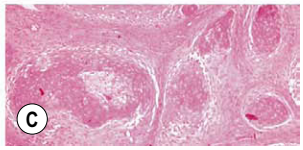


Figure 6.21 Canine multilobular tumor of bone. (A) Gross photograph of canine skull showing multilobular tumor of bone on the zygomatic arch. (B) Radiograph of a slab specimen of skull showing neoplastic proliferation on the occipital bone. (C) Photomicrograph showing the multilobular nature of the tumor.

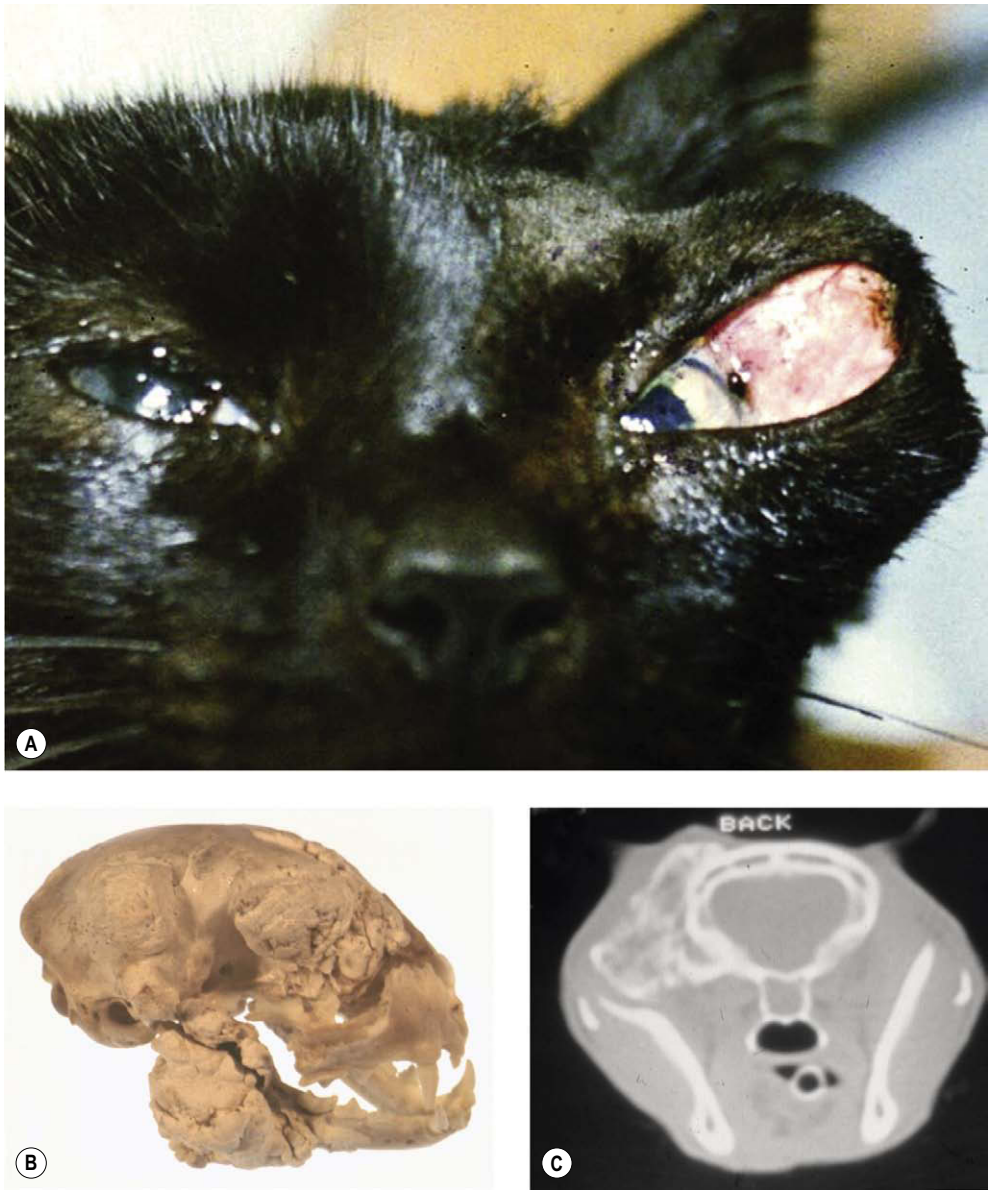


Figure 6.22 Feline osteochondroma, osteochondromatosis. (A) DSH, 11 years old: the firm bony mass, diagnosed as osteochondromatosis, originated from the facial zygomatic bone and deviated the globe nasally. (B) Photograph of a feline skull showing osteochondromatosis lesions on the mandible and on the bony orbit. (C) CT scan of an affected feline skull showing osteochondromatosis in the orbit.

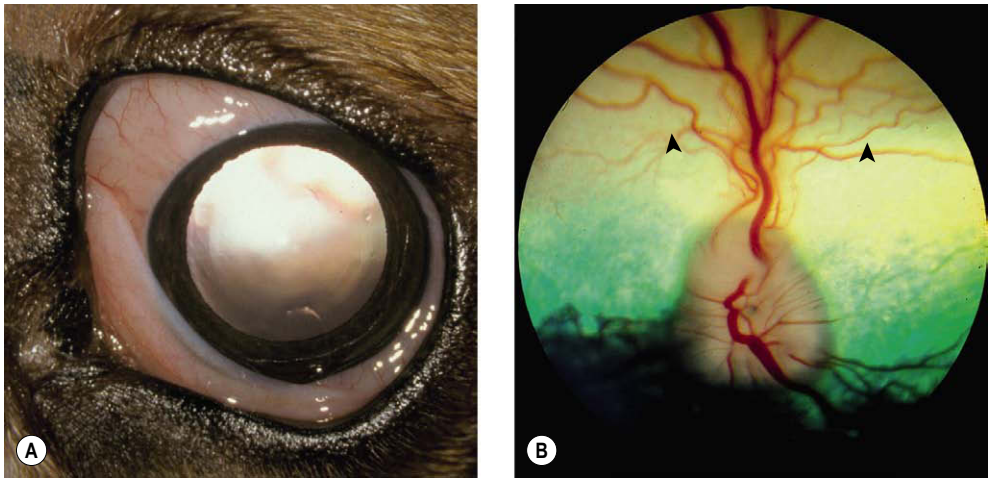


Figure 6.23 Canine orbital meningioma, clinical. (A) Basset Hound, 6.5 years old: the left globe is exophthalmic with moderate chemosis and conjunctival hyperemia. (B) The fundus of the same dog as (A) showing a swollen disc with peripapillary retinal edema. The arrows point to the edge of the globe indentation by the retrobulbar mass, note the subtle change in tapetal color and the change in focal plane of the retinal blood vessels.

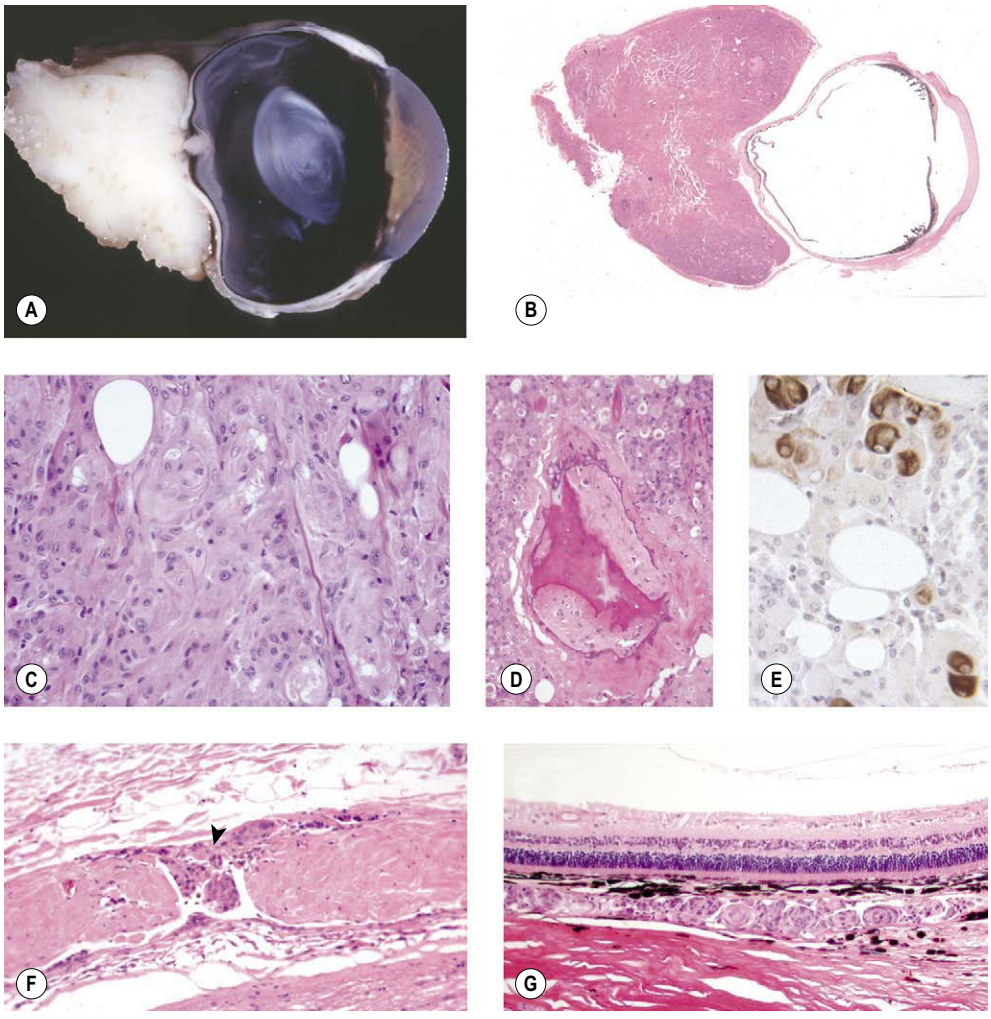


Figure 6.24 Canine orbital meningioma, pathology. (A) Gross photograph of a canine globe with orbital meningioma. (B) Subgross photomicrograph of canine orbital meningioma. (C) Photomicrograph showing the typical appearance of neoplastic cells in canine orbital meningioma. The cells are large with abundant cytoplasm, resembling epithelial cells. (D) Photomicrograph showing a focus of osseous metaplasia within orbital meningioma. (E) Immunohistochemistry showing vimentin-positive meningioma cells. (F) Photomicrograph of the normal canine optic nerve dura mater showing arachnoid cap cells (arrow) extending through the dura mater. Orbital meningioma is thought to arise from these cells. (G) Photomicrograph of the retina and choroid from an affected dog showing spread of tumor into the choroid.

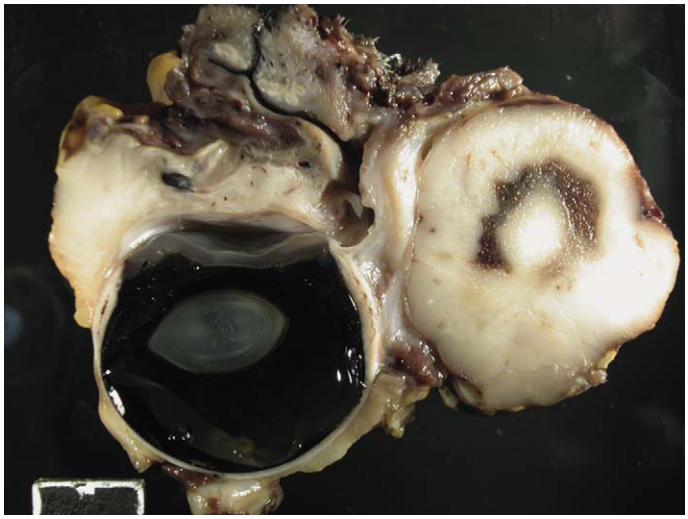


Figure 6.25 Lacrimal gland adenocarcinoma. Gross photograph of a canine globe with orbital lacrimal gland adenocarcinoma.

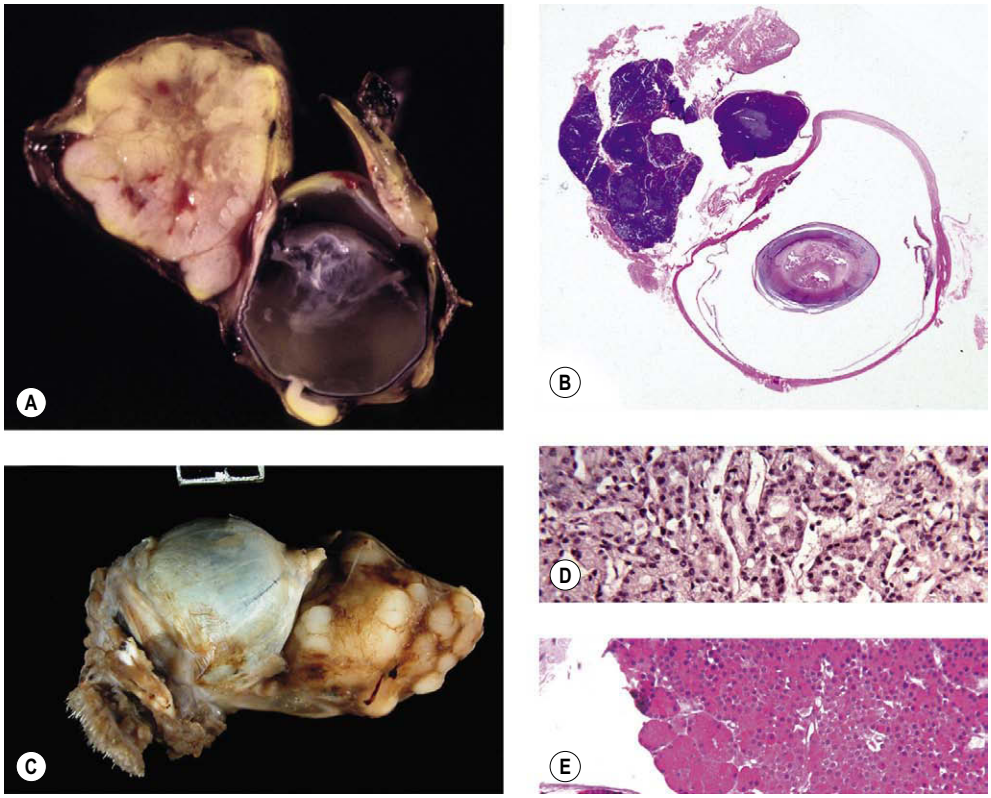


Figure 6.26 Canine lobular orbital adenoma. (A,C) Gross photographs of canine globes and orbital nodules of lobular orbital adenoma. (B) Subgross photomicrograph showing lobular orbital adenoma. (D,E) Photomicrographs showing well-differentiated glandular tissue typical of canine lobular orbital adenoma. PAS stain in (E) showing cytoplasmic secretory material.

- It is not clear in which gland, or glands, the tumor originates, as the tumors can be seen in multiple locations within the orbit

- Morphologic features of diagnostic value include:
  - The tissue submitted for evaluation may consist of only multiple translucent lobules, with no other tissue sampled
  - The neoplastic cells are fully differentiated glandular secretory cells with abundant clear, vacuolated or granular cytoplasm
  - A PAS stain highlights the mucinous nature of the cytoplasmic contents helping to demonstrate the secretory features of the cell cytoplasm
  - Acini may or may not be present, but differentiated ducts are never seen
    - The absence of ducts is a useful feature in distinguishing these tumor nodules from normal glandular tissue
    - In some tumors a few non-neoplastic glandular lobules may be intermingled with several neoplastic lobules further confusing the picture regarding what glandular tissue of the origin of these tumors.

Secondary, metastatic neoplasms (Fig. 6.27)

- Nasal adenocarcinoma
  - Adenocarcinomas often infiltrate into the orbit from the nasal cavity or paranasal sinuses of both cats and dogs
- Metastatic epithelial tumors to the orbit in cats (Fig. 6.27)
  - In cats, but seldom in dogs, hematogenous metastasis may lead to orbital neoplasia
  - These tumors may also invade the globe
  - Likely primary sites include lung, nasal cavity, middle ear, oral cavity, conjunctiva, and mammary gland.

Comparative Comments

In terms of neoplastic diseases of the orbit, similarities exist between those found in the COPLOW collection and those received in human eye pathology laboratories. Lymphoproliferative lesions and leukemia commonly involve the orbit, as do metastatic lesions. The most common epithelial tumors of the lacrimal gland are pleomorphic adenoma, adenoid cystic carcinoma, and malignant mixed tumors. Lymphomas of the lacrimal gland are also common. As is the case in other species, the human orbit contains a variety of structures that give rise to tumors with neurogenic and neural crest differentiation, mesenchymal differentiation, as well as neoplasms arising in bone. Tumors may also involve the orbit by direct extension into the orbit from the sinuses, eyelids, skin, conjunctiva, the eye itself, the optic nerve, the intracranial cavity, and the lacrimal sac.

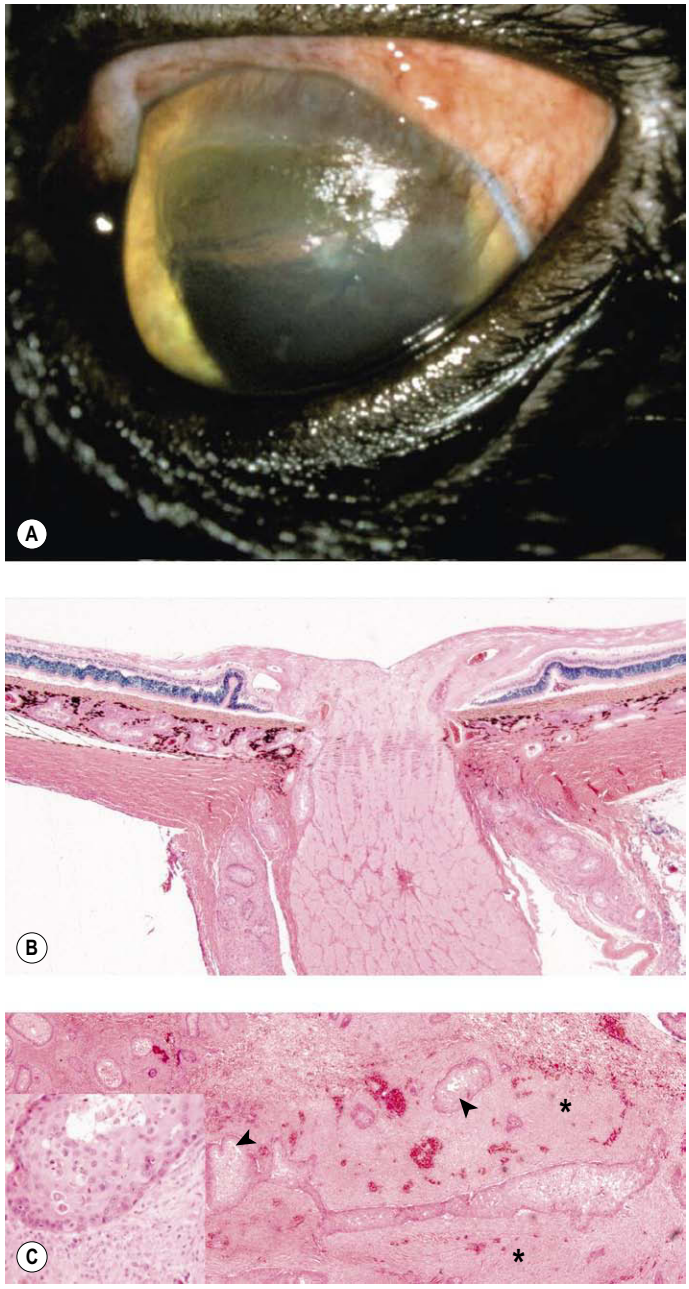


Figure 6.27 Feline orbital metastatic carcinoma. (A) Persian, 12 years old: the tumor resulted in exophthalmia and lagophthalmos. FNA of the superior nasal mass confirmed the diagnosis of squamous cell carcinoma. (B) Low magnification photomicrograph of a feline globe showing metastatic carcinoma in blood vessels adjacent to the optic nerve. (C) High magnification photomicrograph showing neoplastic epithelial cells in vascular structures (arrows) and a desmoplastic stroma (*). The inset is higher magnification.

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Chapter 7

Diseases of the eyelids and conjunctiva

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CONGENITAL ANOMALIES AND EARLY LIFE DISEASES OF THE EYELIDS AND CONJUNCTIVA (Fig. 7.1)

Eyelid agenesis, hypoplasia, coloboma

- This is a sporadic condition, most commonly seen in cats as a segmental agenesis, defect or coloboma of the upper temporal lid
- In addition to eyelid abnormalities, affected cats may have other ocular lesions, including posterior scleral colobomas, choroidal hypoplasia and persistent pupillary membranes. A similar syndrome has also been described in captive Snow Leopards and a Texas Cougar
- The lid defect results in trichiasis, due to mis-directed facial hairs, poor tear film dispersion, or dry eye due to direct corneal exposure. These may all contribute to chronic keratitis
  - Conservative medical management may be beneficial in mildly affected cats, and numerous surgical procedures are described for correction of the defect. Eyes seen in the COPLOW collection have been removed because of chronic corneal irritation.

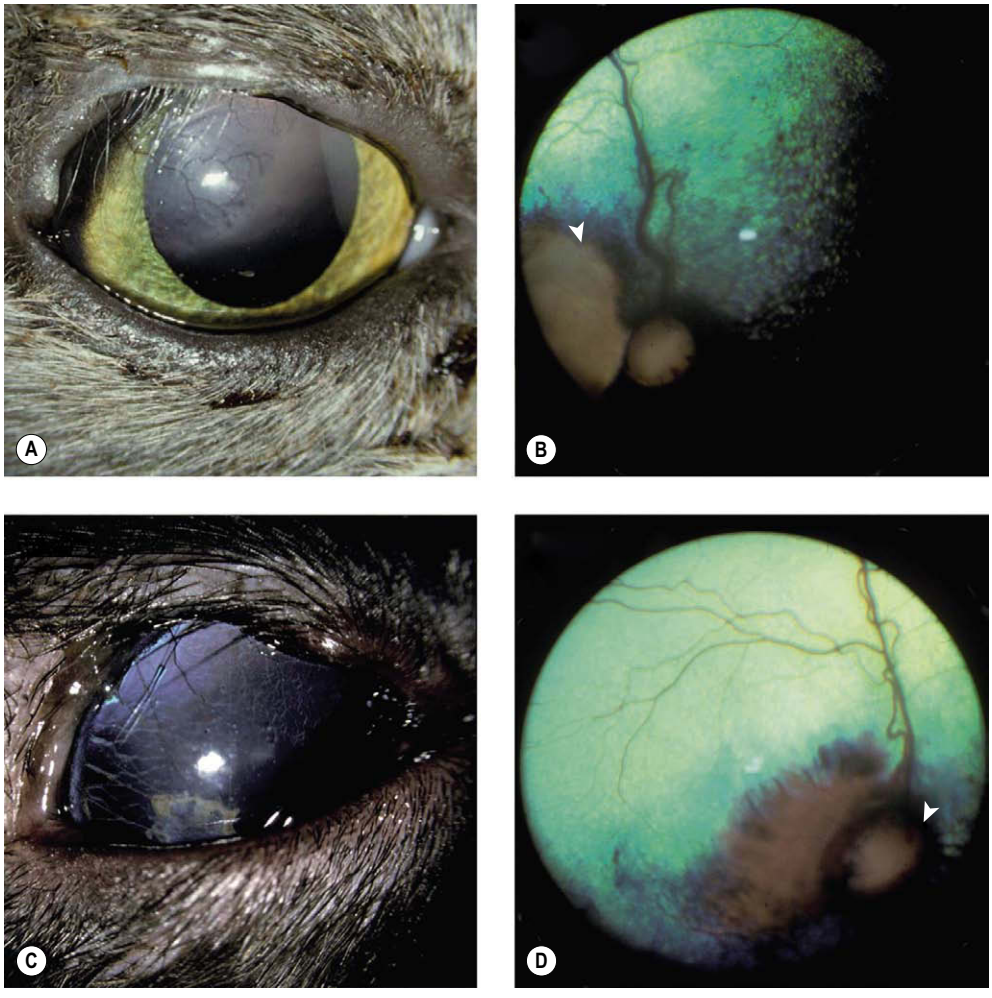


Figure 7.1 Eyelid agenesis with posterior segment coloboma. (A) DLH, 10 months old: agenesis of the superior and lateral lid caused trichiasis and corneal irritation. (B) Fundus of the cat in (A) showing a large temporal coloboma (arrow) of the posterior segment extending to the margin of the optic disc. (C) DSH, 6 months old: the lid defect resulted in trichiasis and a mild corneal irritation. (D) Fundus of the cat in (C) with a peripapillary coloboma of the posterior segment, which affects the optic disc (arrow).

Distichiasis, ectopic cilia and trichiasis

These conditions are common in purebred dogs, and are seldom encountered in other species

- Distichiasis is a condition characterized by abnormally positioned eye lashes/cilia, and is very commonly encountered in dogs
  - The abnormal cilia emerge from the meibomian (tarsal) gland openings on the eyelid margins and make contact with the conjunctival and/or corneal surface causing variable irritation. Distichiasis seldom results in significant corneal disease
- The follicles of ectopic cilia may arise within the meibomian glands, but these cilia emerge on the bulbar surface of the eyelid, through the palpebral conjunctiva
  - Ectopic cilia typically emerge through the central upper eyelid at the 12 o'clock position
  - Unlike distichiasis, ectopic cilia are almost always associated with significant ocular surface irritation. Signs of ocular pain may be of sudden onset, related to the emergence of an ectopic cilia through the palpebral conjunctiva. Significant keratitis, often with ulceration, is a frequent secondary complication of ectopic cilia
- Trichiasis defines a condition in which hairs arising in a normal location are misdirected to contact the ocular surface, e.g. by an abnormality of facial conformation such as prominent nasal folds in the brachycephalic breeds of dog
- Eyes with these diagnoses in the COPLOW collection have been removed because of their secondary complications including severe keratitis, not because of the abnormal cilia or abnormal hair shafts *per se*.

Entropion and ectropion

- Entropion and ectropion are complex conformational defects resulting from:
  - Congenital malformation of the eyelid margins (anatomic) such as excessive eyelid length or laxity or insufficient palpebral fissure length, relative to globe size
  - Acquired disease secondary to neuromuscular dysfunction (atonic) or response to severe ocular pain (spastic)
  - Scar tissue (cicatricial)
- Although very common in certain purebred dogs, these conditions are not described in detail in this text because the eyelid tissue is seldom submitted for evaluation, just the globe which is affected secondarily
- Entropion is defined as an inversion of the eyelid margin
  - Entropion results in trichiasis and corneal disease that is often severe
- Ectropion is defined as an eversion of the eyelid margin
  - Ectropion may lead to exposure of conjunctival surfaces, with secondary conjunctivitis but is rarely a factor in corneal disease. There are no globes in the COPLOW collection where a direct relationship between this eyelid disease and enucleation was expressed on the submission form.

Symblepharon syndrome (Fig. 7.2)

- Symblepharon refers to adhesion or fusion of conjunctival surfaces of the eyelids or third eyelid, to adjacent conjunctival surfaces, or to the cornea. This may lead to obliteration of the conjunctival fornix
- This is usually an acquired condition secondary to severe inflammation that results in loss of integrity of the conjunctival and corneal epithelia
- Symblepharon is most commonly encountered in young cats, in which the cause is usually infection with feline herpesvirus-1 (FHV-1) early in life
- Eyes are most often submitted to the COPLOW collection because of severe corneal involvement, with associated corneal opacity or perforation
- Surgical correction of symblepharon is possible, but prevention of recurrent symblepharon can be a major postoperative challenge.

Conjunctival or corneal dermoid (Fig. 7.3)

- A dermoid is a form of choristoma, a congenital disease characterized by the focal occurrence of fully-differentiated, non-neoplastic tissue in an abnormal location. In this case, skin on the conjunctiva or cornea
- The disorder occurs sporadically in all species. In dogs, the temporal limbus is most commonly affected
- Dermoids are frequently a source of irritation, because of the presence of hair, leading to trichiasis, or they may act as a mass lesion that impacts ocular or eyelid function
- Surgical excision is curative, provided that care is taken to include the deepest margin of the dermoid.

Comparative Comments

Many of the basic differences in the pathology of the human eyelid, as compared with other species, stem from the difference in anatomy. Humans lack a nictitating membrane and do not have a nictitans gland or Harderian gland component to their tears.

Human congenital anomalies of the eyelid, however, do parallel those seen in other species.

- Distichiasis, abnormally positioned eyelashes, is occasionally encountered in man
- Trichiasis, in which cilia in a normal location become misdirected, occurs, most often, as a result of disease rather than breed conformation
  - An example is in the end stages of trachoma, a conjunctival infection by *Chlamydia trachomatis*. The resulting trichiasis, as in animals, abrades the corneal surface, leading to ulceration and scarring and is ultimately a major cause of blindness
  - Another major cause of trichiasis in humans is ocular cicatricial pemphigoid, a chronic disorder that is characterized by recurrent conjunctival surface bullae, which may ultimately result in corneal scarring
- Entropion is distinguished from other disorders that result in lashes misdirected toward the globe by abnormal rotation of the eyelid margin toward the cornea and bulbar conjunctiva. Similar to other species, in humans the underlying cause of the malposition may be congenital, spastic, involutional, or due to scarring
- Ectropion, the turning outward of the eyelid margin away from the globe, in humans may be mechanical, cicatricial, paralytic, or involutional
- For both entropion and ectropion, successful treatment depends on recognition of the underlying pathophysiology.

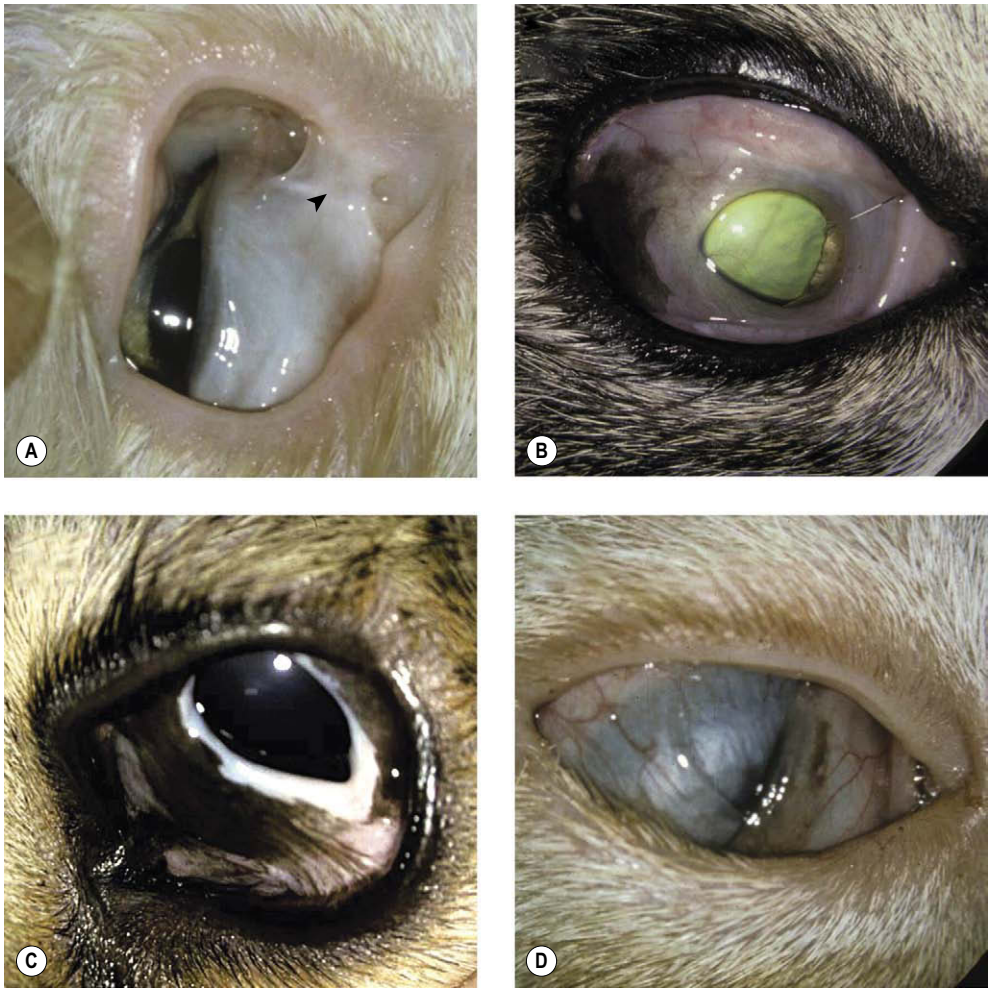


Figure 7.2 Feline symblepharon syndrome. (A) DSH, 1.5 years old: the globe has been manually retropulsed to show a symblepharon (arrow) from the palpebral surface of the nictitans to the superior lid margin. (B) DSH, 9 years old: an extensive symblepharon resulted in visualization of only the central cornea. (C) Bengal, 18 weeks old: the pigmented symblepharon involved the entire medial canthus and nictitans. Both lacrimal puncta were occluded, as was the inferior cul-de-sac. (D) DSH, 18 months old: the thin, translucent symblepharon extended over the entire cornea.

INFLAMMATORY LESIONS OF THE EYELID SKIN

Parasitic dermatitis in horses, cutaneous and ocular habronemiasis, 'summer sores' (Fig. 7.4)

- Nodular cutaneous or conjunctival lesions associated with the larval stage of the nematode parasites *Draschia megastoma, Habronema majus,* or *H. muscae*
  - Adult nematodes infest the gastric glandular mucosa and their larvae are transmitted by flies, e.g. the housefly and stablefly, which serve as intermediate hosts. Larvae in feces are ingested by fly maggots and subsequently deposited on the horse skin, open wounds and mucous membranes from the mouthparts of the feeding adult fly
  - Periocular lesions most frequently involve the medial canthus region
- Histologically, the lesions are characterized by a cavitated lesion containing a predominantly eosinophilic infiltrate, including aggregates of eosinophilic protein around collagen bundles or fragments of parasite larvae.

Demodicosis (Fig. 7.5)

- Cutaneous demodicosis is a cutaneous acariasis caused by *Demodex species* mites. Demodicosis, predominantly due to *Demodex canis* infection, is most often seen as a clinical disease entity in dogs
- Small numbers of mites can be seen in normal skin but clinically affected individuals have large numbers of the parasites
- Mites inhabit the hair follicles, causing excessive keratin secretion and ultimately, a destructive, granulomatous dermatitis
- Localized demodicosis is a relatively common cause of periocular alopecia, erythema and hyperpigmentation in young dogs
- Most cases resolve spontaneously but a small proportion of cases progress to a generalized form of disease, which is frequently complicated by secondary pyoderma
- Clinical demodicosis in adults is most frequently encountered in immune suppressed individuals
- These mites are species-specific and *D. cati* or *D. gatoi*, *D. caballi* and *D. folliculorum* may affect cats, horses or humans, respectively.

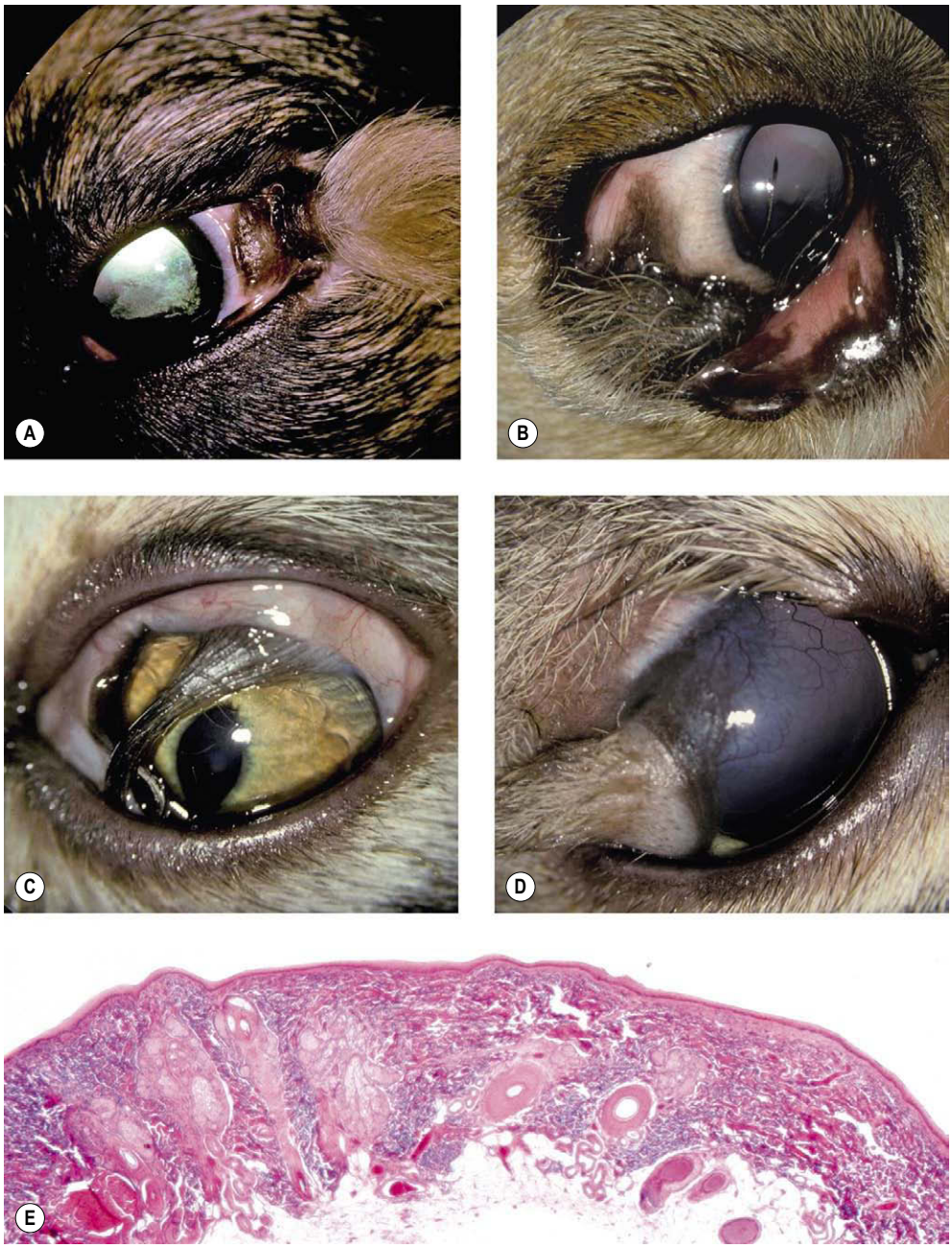


Figure 7.3 Conjunctival dermoid. (A) Mixed Breed, 8 weeks old: the dermoid originated from the temporal bulbar conjunctiva only. Extremely long hairs can be seen. (B) Labrador Retriever, 6 months old: this dermoid involved the bulbar and palpebral conjunctiva. The lower lid and nictitans were also involved. (C) Persian, 13 weeks old: the long hairs from the dermoid are directed across the cornea, but only the conjunctiva was involved. (D) DSH, 1 year old: the lateral bulbar conjunctiva and cornea are involved in this dermoid. A lid agenesis is also present. (E) Photomicrograph showing a conjunctival dermoid with epidermis, follicles, glands, and dermis typical of normal skin.

Dermatophytosis ('Ringworm') (Fig. 7.6)

- The dermatophyte fungi *Microsporum canis, Microsporum gypseum,* or *Trichophyton mentagrophytes* may colonize hair follicles resulting in focal dermatitis. Clinical disease is frequently seen in cats, but is also a relatively common problem in dogs, horses and cattle
- Regional foci of crusting, alopecia or pustular inflammatory reaction are typically seen
- Histologically, fungal elements are seen within or adjacent to the hair shaft and are often associated with furunculosis.

Canine cutaneous histiocytosis, sterile cutaneous granuloma

- This idiopathic granulomatous disease of the canine skin may involve the periocular skin or eyelid margin. The disease is characterized by focal, or multi-focal, nodular lesions. Histologically, granulomatous inflammation is seen, with features of classical granuloma, i.e. a pyogranulomatous center surrounded by epithelioid macrophage cells
- This is considered by some to be the least aggressive condition in a spectrum of histiocytic mass lesions which also includes systemic histiocytosis and malignant histiocytosis

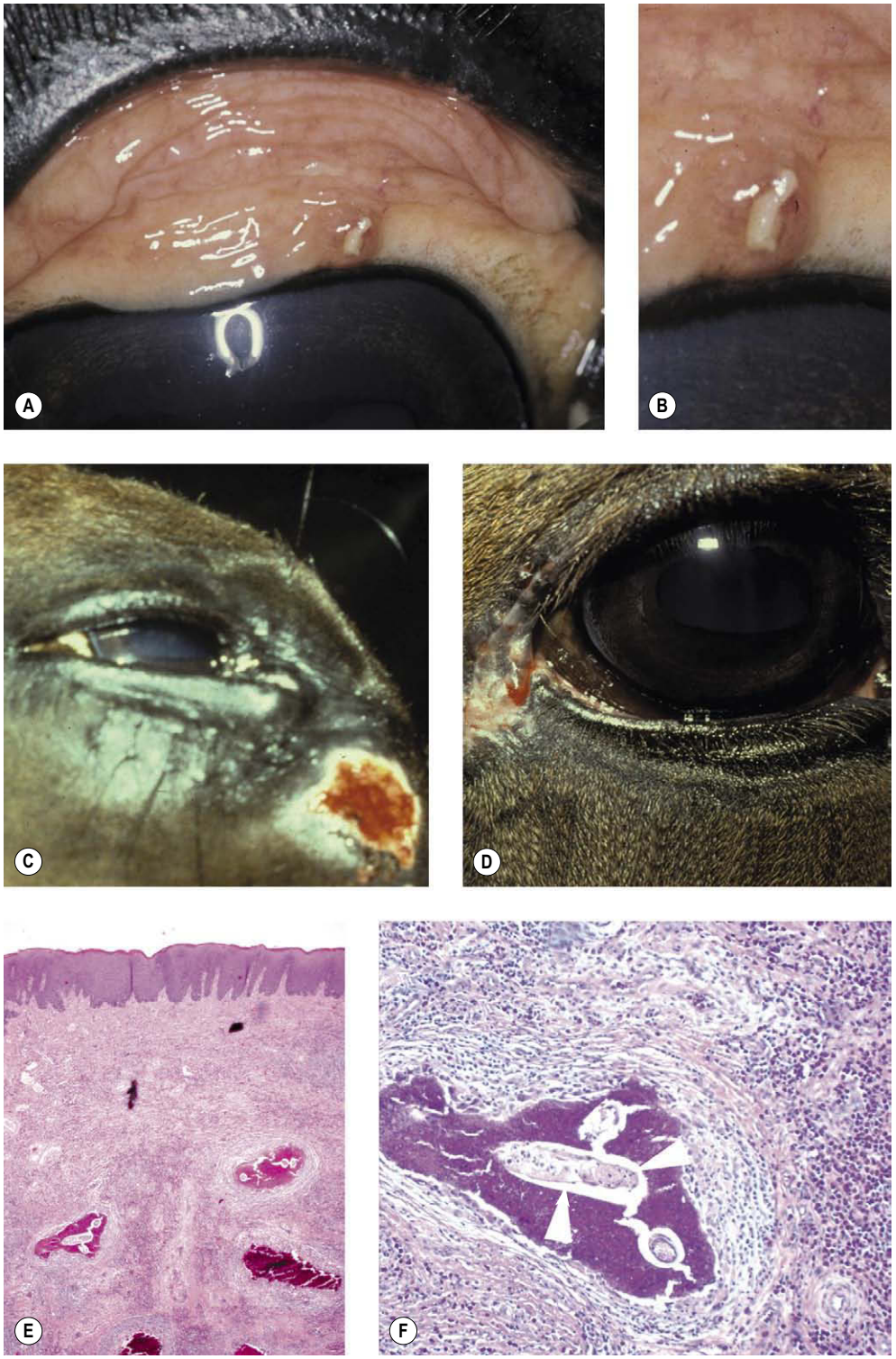


Figure 7.4 Equine habronemiasis. (A) Grade horse, adult: the yellow gritty conjunctival lesion was biopsied to confirm the diagnosis. (B) This is the lesion in (A), magnified. (C) American Saddlebred horse, 10 years old: a large erosive lesion is present near the medial canthus. (D) Thoroughbred, adult: the medial canthus was involved in both eyes. (E) Photomicrograph showing dermal and subcutaneous eosinophilic, granulomatous inflammation. (F) Remnants of intact nematodes (arrows) are present in this section.



Figure 7.5 Demodicosis. (A) DLH, 13 years old: this diabetic cat had an exudative blepharitis and medial canthus erosion. (B,C) Photomicrographs showing hair follicles dilated with keratin debris and Demodex mites.

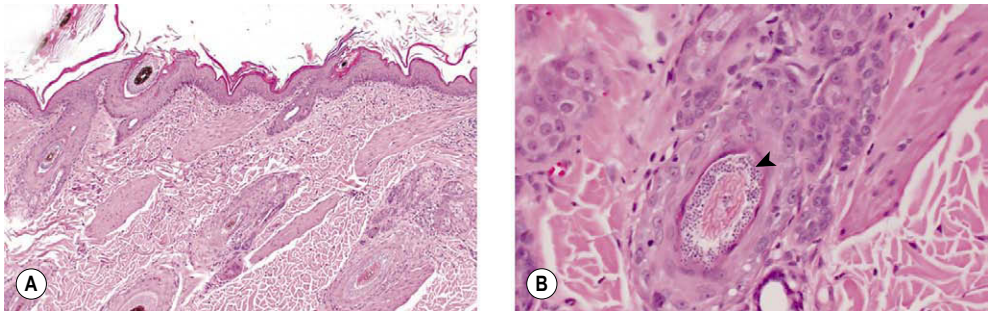


Figure 7.6 Dermatophyte infection. (A,B) Photomicrographs showing hair follicles containing dermatophyte fungi within and adjacent to the hair shaft (arrow), and surface hyperkeratosis.

- In the interest of caution and completeness, this diagnosis should always be made only after first ruling out infectious causes of granulomatous disease by using special stains for bacteria and fungi.

Miscellaneous other causes of blepharitis:

- Other infectious causes of blepharitis include:
  - *Staphylococcus* spp.
  - In endemic areas, such as the Mediterranean countries and South and Central Americas, Leishmaniasis frequently involves the periocular skin
- Atopy and auto-immune diseases, including pemphigus complex disorders and uveodermatologic syndrome (for detailed discussion of the latter, see Ch. 9)
- Detailed consideration of periocular dermatoses is outwith the scope of this text. The reader is referred to a veterinary dermatopathology text for more detailed discussion of specific skin diseases.

Comparative Comments

- Diffuse inflammation of the lids, termed blepharitis, occurs commonly in humans and is caused by either seborrheic dermatitis or a chronic bacterial infection
- A hordeolum, also commonly seen in man, is an acute purulent inflammation of either the superficial eccrine or sebaceous glands (external hordeolum, or stye) or the meibomian glands (internal hordeolum) of the eyelids
- Chalazia, together with hordeolum, constitute one of the most common causes of lid swelling in people. A chalazion is a chronic, lipogranulomatous inflammation in the tarsus, resulting from an obstruction in the meibomian gland ducts, often with secondary bacterial infection
- Other bacterial infections of note in humans include *Mycobacterium leprae* and the synergistic infection of *Streptococcus pyogenes* and *Staphylococcus aureus*, which may result in necrotizing fasciitis, a disease that causes massive destruction of the eyelid and adjacent orbital tissue
- The principal viral infections of the human eyelid are molluscum contagiosum, an infection caused by a poxvirus, that leads to formation of small, discrete waxy papules with umbilicated centers; verruca vulgaris, papillomatous lesions caused by the human papillomavirus; and herpes simplex, herpes varicella, and herpes zoster, all of which begin as vesicles or blisters on an erythematous base.

PROLIFERATIVE AND NEOPLASTIC LESIONS OF THE EYELID SKIN

Canine juvenile cutaneous histiocytoma (Figs 7.7, 7.8)

This is a common, benign, typically self-limiting, mass lesion on the haired skin of dogs. There are 38 cases in the COPLOW collection. Canine juvenile cutaneous histiocytoma is predominantly seen in young dogs, decreasing in frequency in dogs older than 3 years.

- The purported cell of origin is the cutaneous antigen-presenting macrophage known as the Langerhans cell
- Grossly, the lesions are characterized by a well-circumscribed, round flattened nodule with hair loss and often central, superficial ulceration
- Histological features
  - The characteristic histiocytic cells are mixed with a variable population of lymphocytes
    - Lymphocytes often make up the majority of the cellular infiltrate
    - The lymphocytic infiltrate is often most prominent at the deepest extent of dermal involvement and les prominent superficially
  - The histiocytic component infiltrates between pre-existing collagen bundles, often forming single-file rows of cells
  - The characteristic cells are often seen invading the epidermis or follicular epithelium as individual cells, or in small aggregates.

Cutaneous and systemic histiocytosis (Fig. 7.9)

There are 18 cases in the COPLOW collection. Four are in Bernese Mountain dogs and four are in Labrador Retrievers.

- Cutaneous histiocytosis (see above) and systemic histiocytosis represent the regional proliferation of histiocytes. There is little agreement regarding the malignant potential of these conditions, however systemic histiocytosis has the potential to recur or to spread
- Cutaneous histiocytosis is less likely to spread beyond the skin whereas systemic histiocytosis is likely to lead to signs of systemic disease
- Both forms are reported to be familial in the Bernese mountain dog, but the disease is not limited to this breed (see above)
- Ocular lesions may include masses within the eyelid skin or episclera, exophthalmos, uveitis, retinal detachment and glaucoma
- Both diseases are characterized by a deep intra-dermal and subcutaneous infiltrate of large histiocytes, lacking the features of classical granulomatous inflammation
- The characteristic cells in cutaneous histiocytosis are bland and demonstrate few features of malignancy
- The characteristic cells of systemic histiocytosis have only mildly anaplastic features and may also show a dramatic vasocentric tendency and reticulin deposition.

Canine cutaneous melanocytic tumors (melanocytoma) (Fig. 7.10)

Cutaneous melanocytic tumors in dogs are almost always benign melanocytomas. There are 27 cases in the COPLOW collection.

- The superficial dermis is effaced and infiltrated with neoplastic spindle cells, polygonal cells, or large round cells which are usually, but not always, heavily pigmented
- Individual or tight clusters of neoplastic cells are seen immediately below the epidermis or within the epidermis or follicular epithelium
  - This feature does not suggest malignancy
- Malignant melanomas of the haired skin are seen rarely and should only be diagnosed upon identification of compelling anaplastic cellular features and evidence of aggressive infiltration.

Feline cutaneous melanocytic tumors

Although cutaneous tumors of melanocytic origin are rare in cats, they are often very malignant in their biological behavior, despite the fact

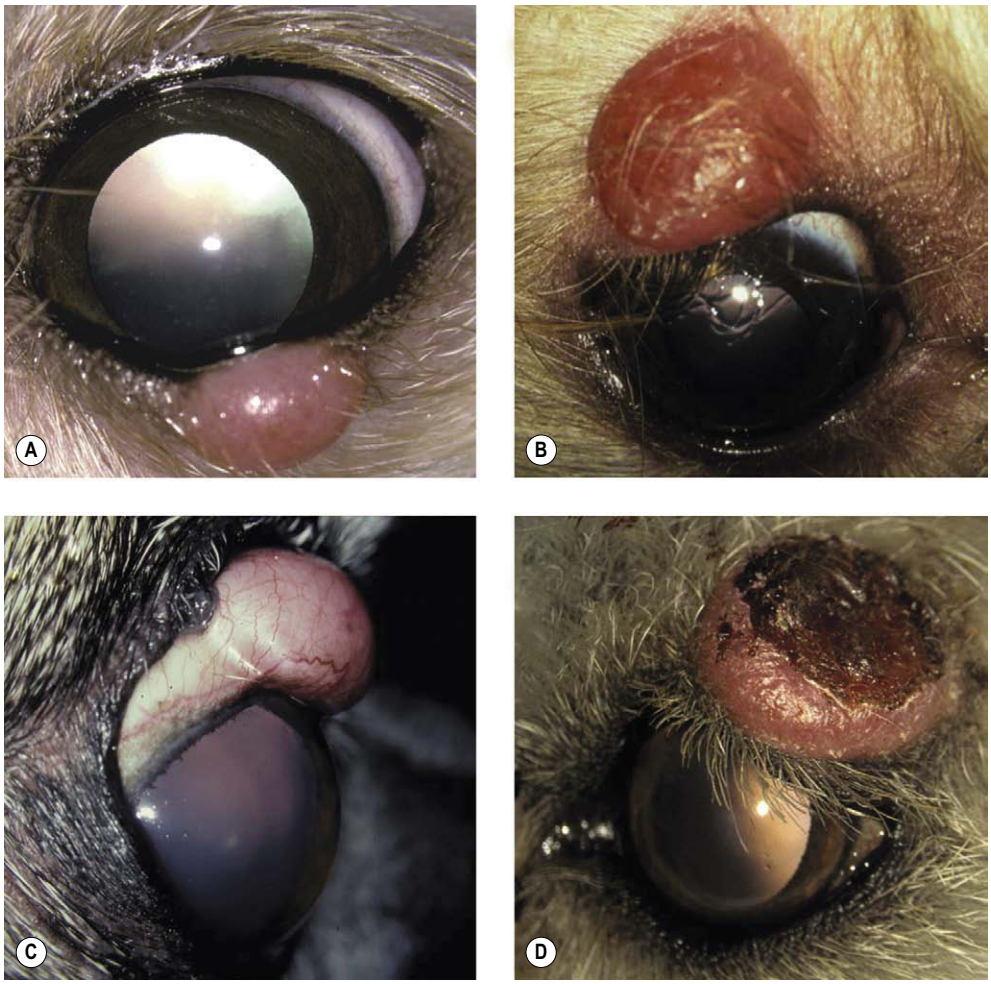


Figure 7.7 Canine cutaneous histiocytoma, clinical. (A) Mixed Breed, 5 years old: lower lid margin is involved with a smooth pink mass. (B) Yorkshire Terrier, 4 years old: there is a very hyperemic mass on the superior lid margin. (C) Pug, 3 years old: the mass originated from the bulbar conjunctiva. (D) West Highland White Terrier, 6.5 years old: an erosive surface is visible on this mass.

that their cytologic features may not be particularly alarming. There is only one case in the COPLOW collection.

Comparative Comments

- In humans, benign melanocytic disorders and tumors involving the lid include ephelides or freckles, lentigo, nevocellular nevi, blue nevi, nevus of Ota, and compound nevus of Spitz
- The malignant melanocytic tumors in humans are generally divided into four major subtypes of cutaneous malignant melanoma: lentigo maligna melanoma, acral lentiginous melanoma, superficial spreading melanoma, and nodular melanoma. Several rare variants of malignant melanoma are also seen.

Intradermal epithelial cysts (Fig. 7.11)

- Epidermal inclusion cyst: stratified squamous epithelial lined cyst with keratin accumulation
- Follicular cyst: the anatomic location of the cyst is suggestive of origins in an isolated or obstructed hair follicle
- Dermoid cyst: containing additional epithelial differentiation of hair follicle and/or glandular elements.

Comparative Comments

The principal cystic lesions affecting the eyelid in humans are:

- Epidermoid cysts (present at birth)
- Epidermal inclusion cysts (acquired but otherwise identical to epidermoid cysts)
- Dermoid cysts (which include adnexal structures)
- Sweat gland cysts.

Cutaneous sebaceous adenoma/epithelioma (Fig. 7.12)

- These are benign tumors of sebaceous glands occurring commonly in dogs, which are also recognized in cats
- Adenoma is a very common periocular tumor and is largely made up of fully differentiated sebaceous glandular tissue
  - Some pathologists make a distinction between sebaceous adenoma and sebaceous hyperplasia based on the orientation of the secretory tissue around the duct. If the duct is appropriately positioned it is typical of hyperplasia
  - Sebaceous adenoma is frequently exophytic, or even papillary, in appearance, often with central cavitation

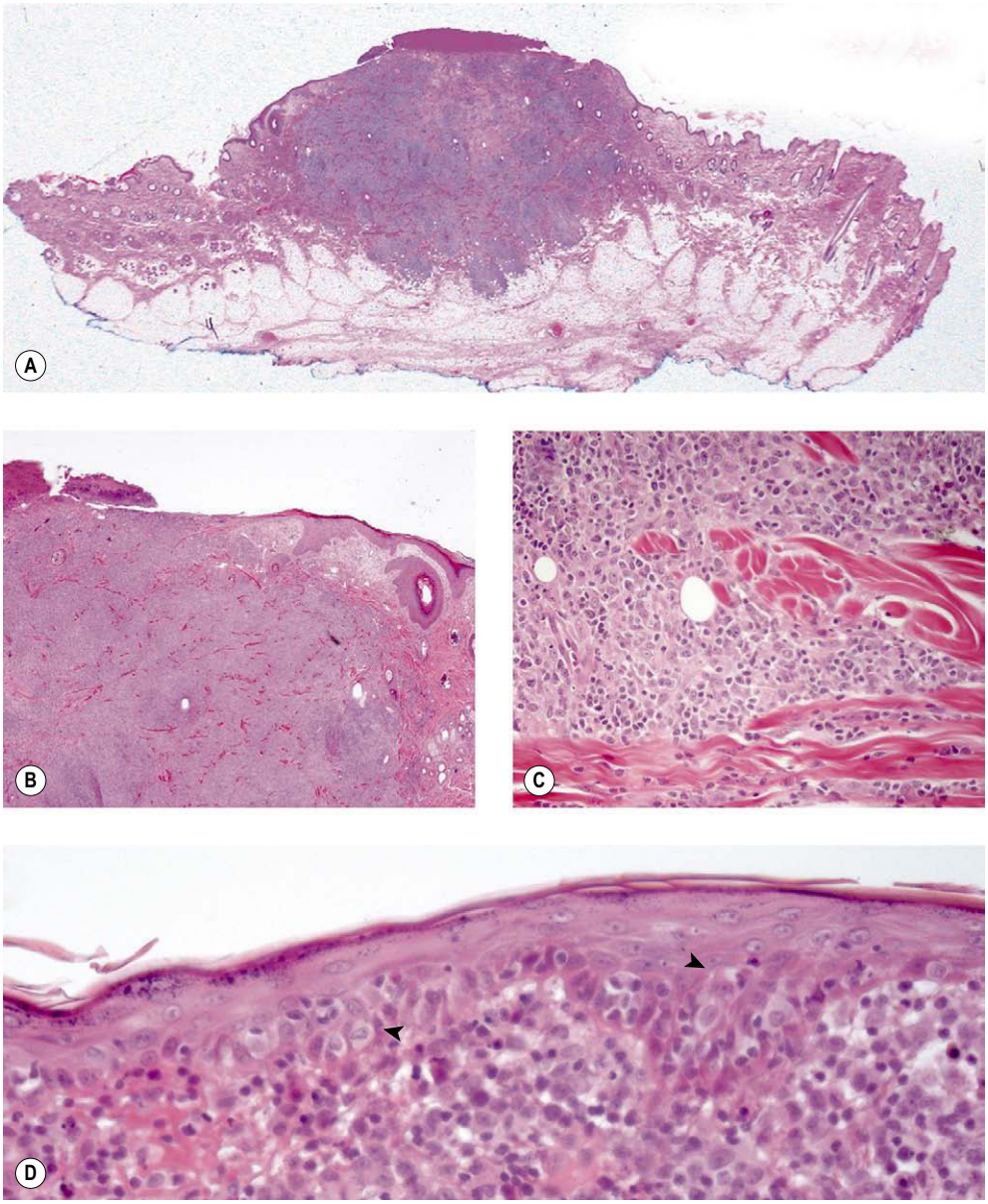


Figure 7.8 Canine cutaneous histiocytoma, pathology. (A) Low magnification photomicrograph of canine juvenile cutaneous histiocytoma. A dermal infiltrate causes a raised, ulcerated, and cellular mass lesion. (B) Higher magnification of the margins of the mass. The infiltrate abuts the epidermis and fills the space between dermal collagen bundles in the dermis. (C) Higher magnification showing histiocytic cells pushed between pre-existing collagen in the dermis. (D) Photomicrograph showing the histiocytic cells abutting the epidermis and individual or small clusters of histiocytic cells within the stratum basale (arrows).

- Epithelioma is mainly composed of undifferentiated basal cells, with occasional areas of sebaceous or squamous ductular differentiation
- Surrounding lipogranulomatous inflammation may accompany both tumor types.

Canine trichoblastoma (basal cell tumor) (Fig. 7.13)

- Trichoblastoma is a common benign tumor occurring on the head and neck of dogs
- The tumor replaces tissue of the dermis with a distinct loose cellular stroma, and cords, ribbons or nests of poorly-differentiated epithelium reminiscent of hair bulb epithelium.

Trichoepithelioma (Fig. 7.14)

- This is an epithelial tumor of hair follicular origin
- The neoplasm is often continuous with the surface epidermis and extends deeply into the dermis showing variable features of hair follicle differentiation.

Canine infundibular keratinizing acanthoma (intracutaneous epithelioma, keratoacanthoma) (Fig. 7.15)

- This benign neoplasm remains connected to the epidermis by a stalk or pore and forms a central core of solid keratin with prominent keratin pearls.

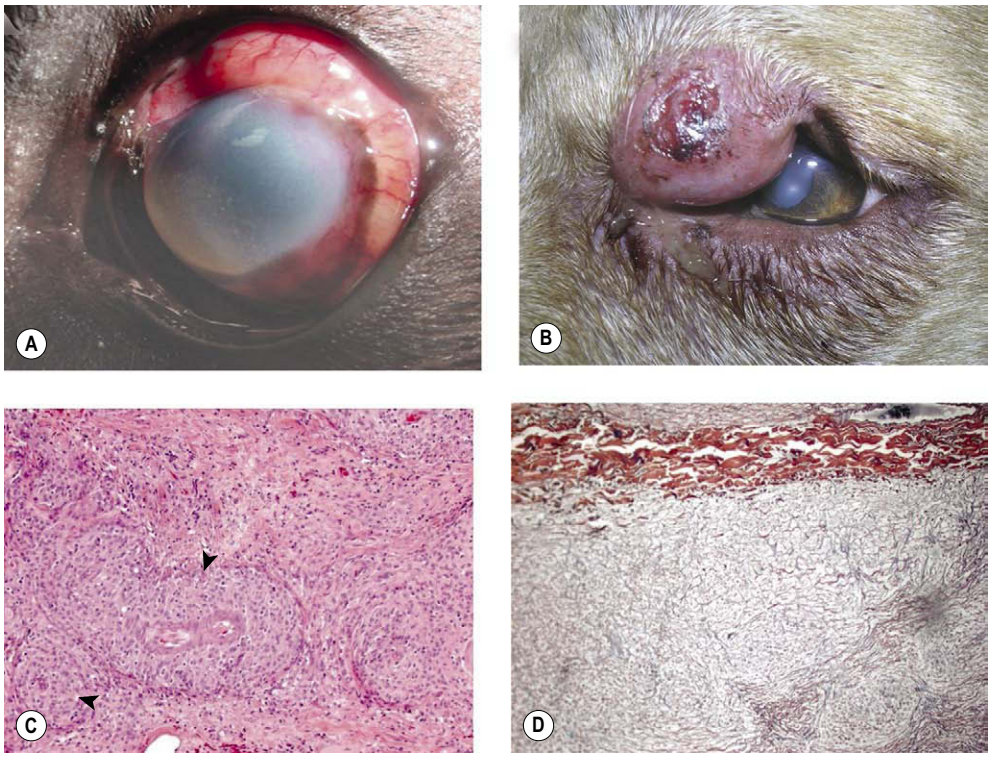


Figure 7.9 Systemic histiocytosis. (A,B) Mass lesions in the episcleral tissue accompanied by corneal edema (A) and eyelid (B) were caused by systemic histiocytosis. (B, courtesy of Jane Cho.) (C) Photomicrograph showing extensive solid sheets of histiocytic cells. There is a marked vasocentric histiocytic infiltrate (arrows), which is a strong diagnostic indicator of systemic histiocytosis. (D) Photomicrograph showing reticulin fibers surrounding individual neoplastic histiocytes (Snook reticulin stain).

Canine sweat gland adenoma (Fig. 7.16)

- Cyst adenoma: this tumor is usually very well-differentiated and made up of multiple widely dilated cysts filled with watery fluid
- Sweat gland adenoma: this tumor is a nodular, solid to cavitated dermal mass which typically shows clear apocrine glandular differentiation
  - Look for evidence of a double cell lining of the glandular structures
  - Occasionally, these tumors have a component of myoepithelial cell proliferation (complex adenoma) or cartilage/bone differentiation (mixed adenoma).

Feline apocrine gland tumor (Fig. 7.17)

- This is a common dermal mass lesion, which is frequently cavitated
- The tumor is a solid mass of poorly-differentiated epithelial cells showing glandular features, often with focal areas demonstrating prominent doubling of the glandular epithelium. There can also be a myoepithelial component to the tumors making them a complex tumor or a mixed tumor
  - Because these tumors are poorly-differentiated, they are often referred to as adenocarcinoma, but they are benign in their biologic behavior.

Apocrine cystadenomas in Persian cats (hidrocystomas) (Fig. 7.18)

- These multifocal, pigmented, nodular lesions on the eyelids are most often seen in Persian cats
- Each lesion is made up of one or more dilated epithelial cysts
  - Based on the position of the cystic tumors and the cuboidal nature of the epithelial cells, these cysts are thought to arise from sweat glands
- The cysts are filled with thick brown material and often a predominantly histiocytic cellular infiltrate
- There is a potential for additional lesions to occur at other sites on the eyelids following excision.

Canine mast cell tumors (Fig. 7.19)

- One of the most common cutaneous or subcutaneous tumors of the dog
- Their clinical appearance on the eyelid is no different from other sites on the integument
- Surgical management of peri-ocular mast cell tumors is complicated by the difficulty in obtaining sufficiently wide margins in this location, while preserving ocular function
- There is a morphological grading scheme consisting of three grades, from grade 1 (most benign) to grade 3 (most malignant).

Grade 1 mast cell tumor

- A well-defined, circumscribed nodule located entirely within the dermis.
- Well-differentiated neoplasm:
  - Oval cell shape with little or no cellular pleomorphism
  - Oval, bland, centrally-positioned nuclei
  - Abundant metachromatic cytoplasmic granules
  - Small nucleus to cytoplasm ratio

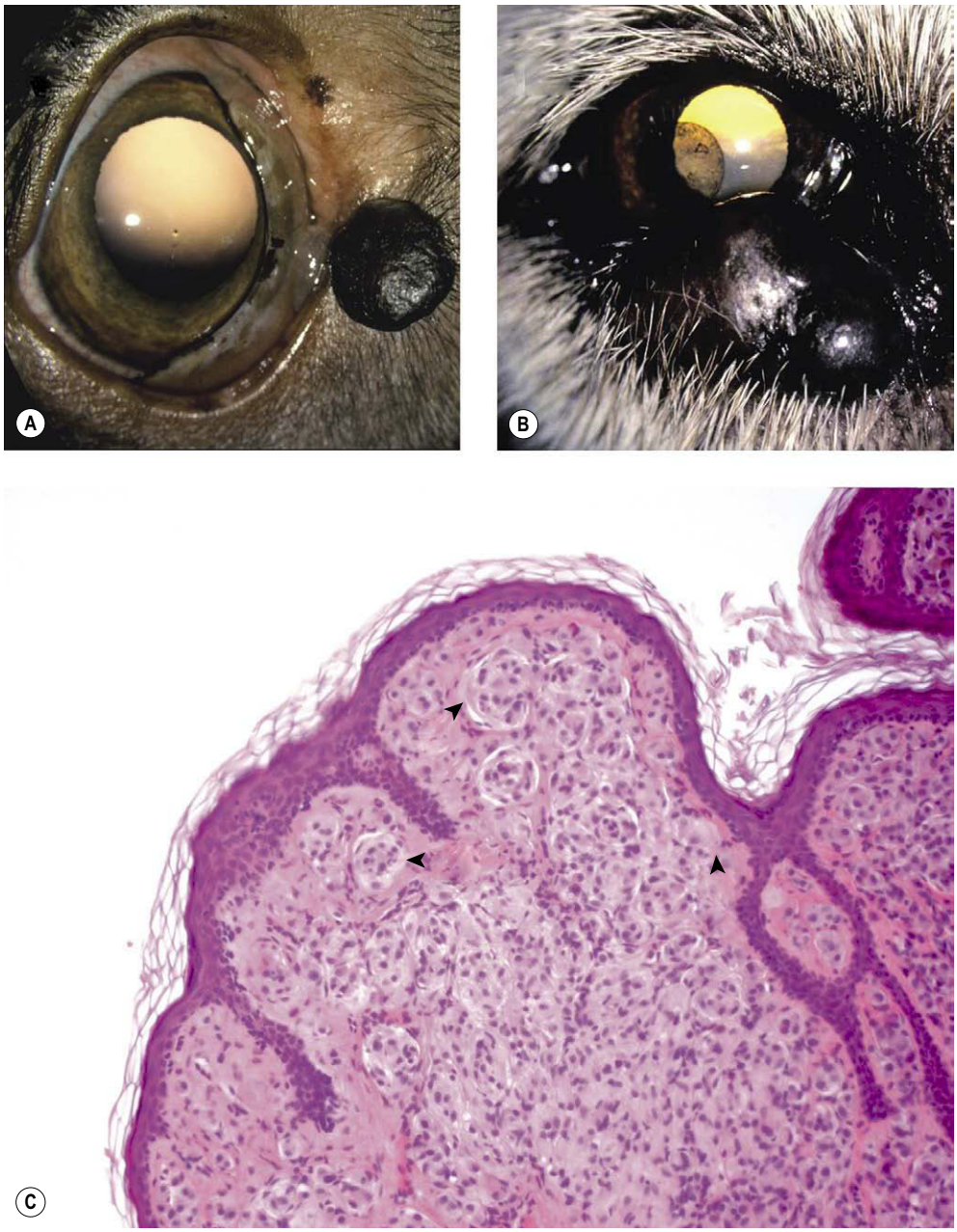


Figure 7.10 Canine melanocytic cutaneous tumors. (A) Doberman Pinscher, 5 years old: this well-delineated mass on the lid margin was confirmed to be a melanocytoma. (B) Golden Retriever, 10 years old: this poorly-delineated lobulated mass involved the inferior lid and medial canthus. The mass was confirmed to be a melanoma. The translucent spherical mass in the pupil is a uveal epithelial cyst. (C) Photomicrograph showing non-pigmented clusters of neoplastic melanocytes abutting the epidermis (arrows).

- No mitotic activity
- Little or no remodeling of the stroma.

Grade 2 mast cell tumor

- The morphologic features of grade 2 mast cell tumor are intermediate between those of grade 1 and grade 3 tumors.

Grade 3 mast cell tumor

- Extends deeply into the subcutaneous tissue, and may not be present in the dermis at all
- Cellular characteristics of anaplasia, and may not be readily recognizable as mast cells:
  - Highly variable nuclear shape and nuclear size
  - Large nucleus to cytoplasm ratio
  - Few metachromatic cytoplasmic granules
  - Prominent, large and variably shaped nucleoli
  - Easily detected mitotic activity
  - Extensive stromal remodeling
    - Abundant , glassy collagen
    - Pronounced tissue edema
    - Areas with scant neoplastic cells.

Feline mast cell tumors (Fig. 7.20)

- One of the most common skin tumors of cats
- Occur anywhere on the skin, with neither predilection for, nor specific characteristic appearance or behavior in, the periocular region
- Primary feline mast cell tumors are typically small and occur in the dermis. Morphologically, they resemble the grade 1 mast

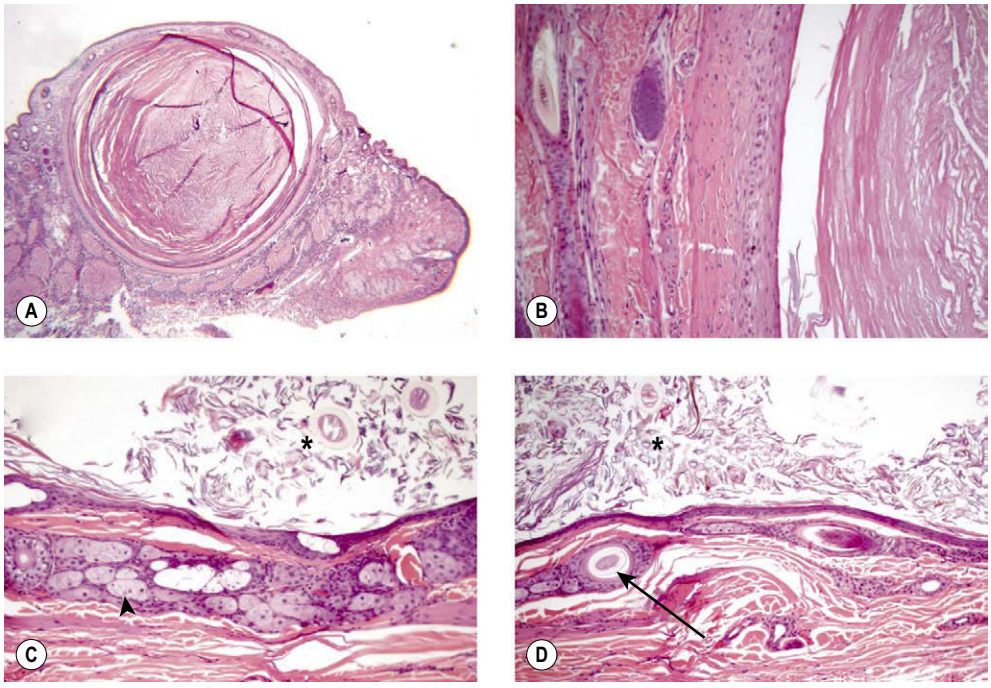


Figure 7.11 Epithelial inclusion cyst and dermoid cyst. (A) Low magnification photomicrograph showing an epithelial inclusion cyst in the dermis of the eyelid. The circular cyst is lined by stratified squamous epithelium and filled with keratin. (B) Higher magnification showing the epithelium and the keratin deposited in the cyst center. (C,D) Photomicrographs showing a dermoid cyst (*), its lining and differentiated sebaceous glands (arrowhead) and hair follicles (arrow).

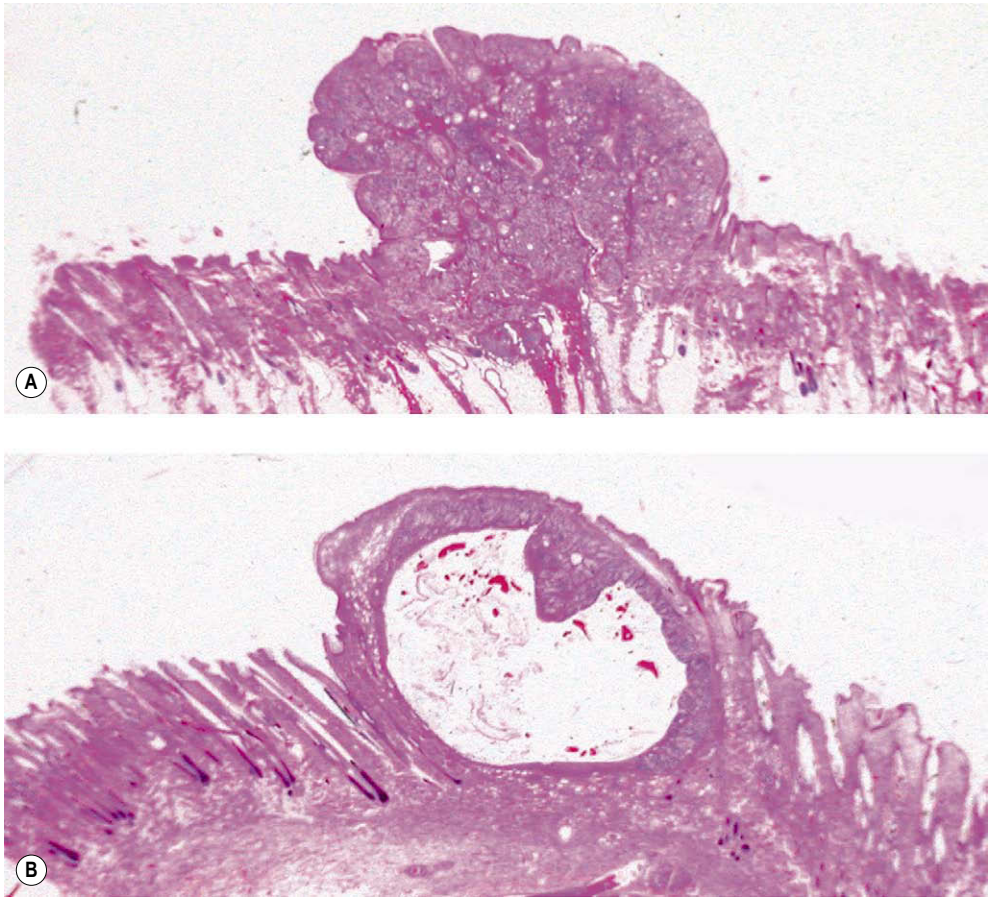


Figure 7.12 Sebaceous adenoma. (A,B) Low magnification photomicrographs of this exophytic neoplasm showing solid (A) and cystic (B) forms.

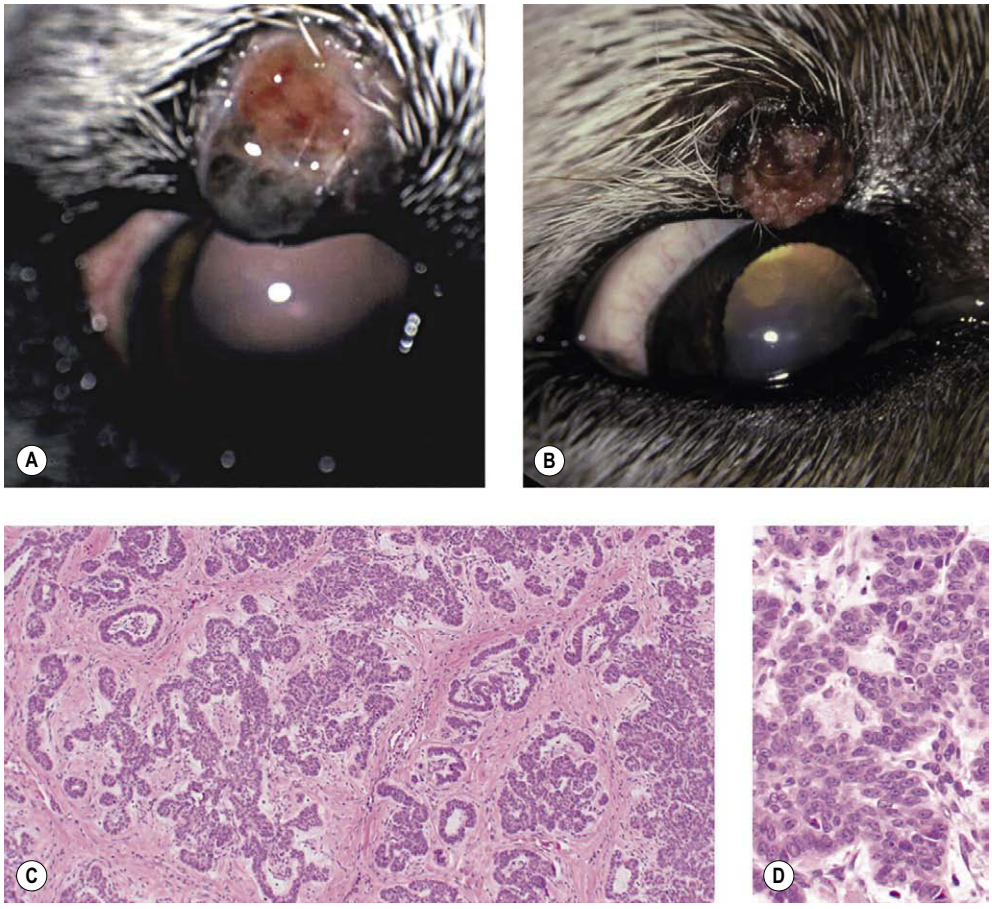


Figure 7.13 Trichoblastoma, canine. (A) Great Dane, 12 years old: the mass was pigmented and ulcerated. (B) Golden Retriever, 10 years old: this ulcerated, non-pigmented mass was lobulated. (C) Photomicrograph showing cords of poorly-differentiated epithelium radiating from a central aggregate. The stroma is characteristically loose and sparse in collagen. (D) Higher magnification photomicrograph showing the poorly-differentiated epithelium.

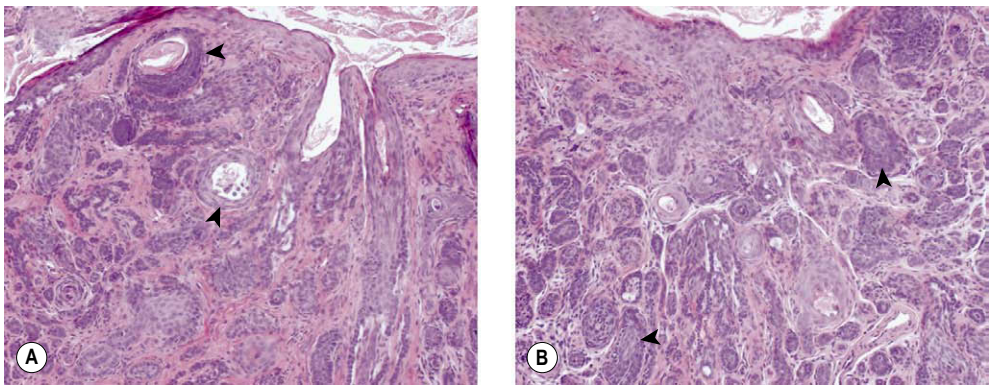


Figure 7.14 Trichoepithelioma. (A,B) Photomicrographs showing neoplastic epithelial structures remotely suggestive of hair follicle differentiation (arrows).

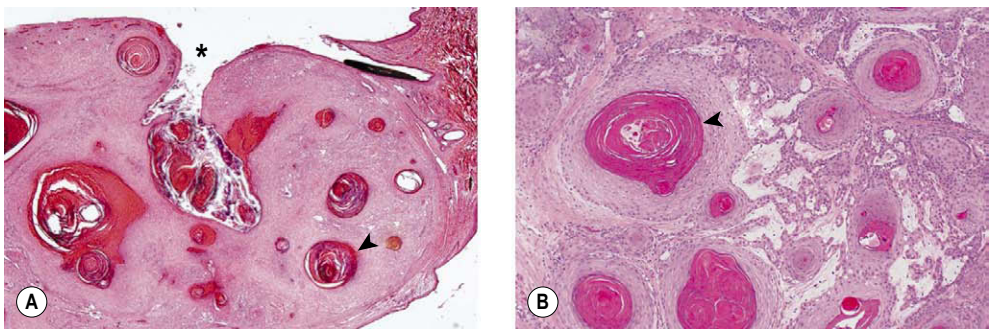


Figure 7.15 Infundibular keratinizing epithelioma. (A,B) Photomicrographs showing a neoplastic epithelial tumor connected to the surface by a pore (*) and characterized by prominent squamous pearls (arrows).

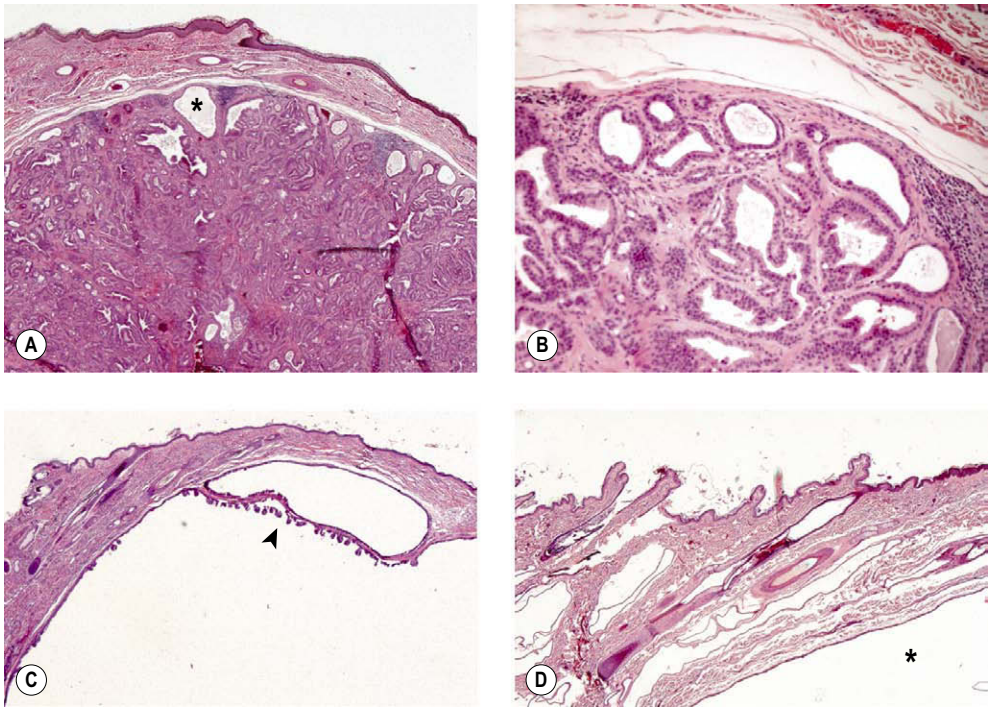


Figure 7.16 Canine sweat gland adenoma. (A) Photomicrograph of a solid tumor with numerous glandular lumina (*). (B) Higher magnification, of the tumor depicted in (A), showing the glandular structures. (C) Cystic tumor with papillary epithelial structures (arrow). (D) In this fully differentiated tumor the sweat glands are markedly dilated (*).

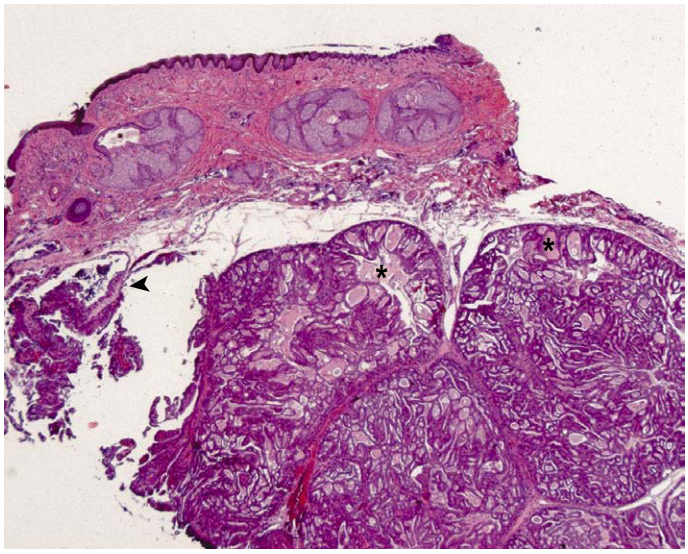


Figure 7.17 Feline sweat gland tumor. Photomicrograph showing a solid tumor with small glandular lumina (*) and other areas that are more cystic (arrow).

cell tumor of dogs, but there is no grading system for feline mast cell tumors

- These tumors often recur at other sites, and visceral involvement (spleen, liver, bone marrow), although less common than cutaneous involvement, is more likely than with canine mast cell tumors
- The 'histiocytic' subtype occurs in younger cats and is rare
  - 'Histocytic' feline mast cell tumors are composed of neoplastic cells with abundant cytoplasm and few cytoplasmic granules, that are difficult to recognize as mast cells.

Epitheliotropic lymphoma (mycosis fungoides) of the eyelid skin (Fig. 7.21)

There are 10 cases of epitheliotropic lymphoma involving the eyelid skin in the COPLOW collection.

- Epitheliotropic lymphoma (mycosis fungoides) of the eyelid has been reported to resemble blepharo-conjunctivitis in dogs
- This tumor is, characteristically, a T-cell lymphoma arising in the dermis. The hallmark of this form of lymphoma is the invasion of the epidermis and/or follicular epithelium by neoplastic cells, often aggregated in clusters referred to as Pautrier's microabscesses.

Peripheral nerve sheath tumors (PNST) in cats (Fig. 7.22)

There are 25 cases in the COPLOW archive, representing 1% of feline ocular tumors.

- The feline eyelid appears to be particularly at risk for developing this tumor
- The designation of PNST is based on recognition of a characteristic morphologic and immunohistochemical appearance:
  - This is a low grade (usually grade 1) spindle cell tumor with features of Antoni A or Antoni B cellular organization
    - The Antoni A cellular pattern is characterized by spindle cells arranged in such a way that the nuclei line up to make rows or palisades, leaving adjacent areas free of nuclei

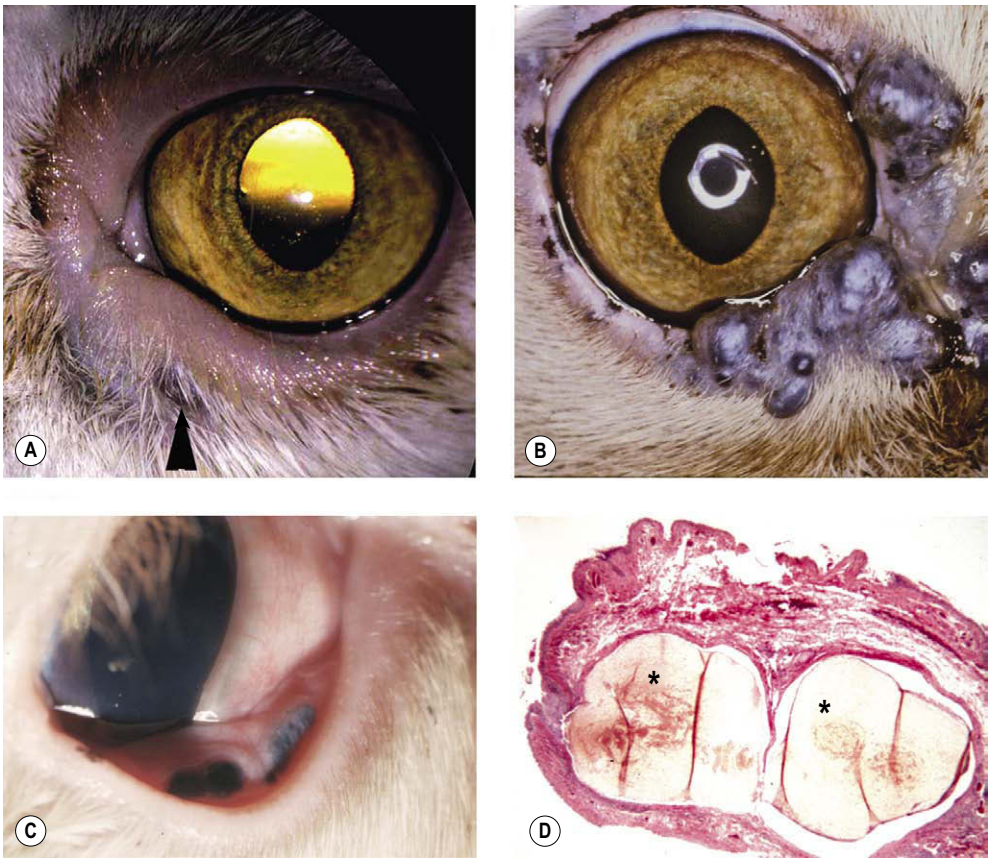


Figure 7.18 Apocrine cystadenoma/apocrine hidrocystoma. (A) Persian, 1 year old: this early case has a black focal discoloration of the lid (arrow) with minimal elevation. (B) Persian, 8 years old: advanced case with multiple elevated lesions. (C) Clinical photograph showing cysts visible on the palpebral conjunctival surface. (D) Low magnification photomicrograph showing a cyst lined by a thin epithelium and filled with cell-poor pigmented secretory material (*).

  - The Antoni B cellular pattern is a more random distribution of cells with a diffuse mixing of cell bodies and delicate collagen and myxoid stroma
- Characteristic immunohistochemistry profile:
  - Vimentin positive
  - S100 positive
  - Collagen IV positive
  - Laminin positive
- PNST of the eyelid is a locally infiltrative tumor, requiring wide margins of excision that may necessitate enucleation, but is unlikely to metastasize.

Equine sarcoid and bovine fibropapilloma (Fig. 7.23)

Both of these common, cutaneous proliferative diseases are thought to be caused by bovine papilloma virus.

- Equine sarcoid is a very common peri-ocular tumor
  - Sarcoid is more common in young horses
  - The clinical/gross appearance is highly variable. While sarcoid may be categorized into as many as six different subtypes based on clinical appearance, it is not easy to hold to these carefully defined categories. The spectrum of disease may be summarized as follows:
    - Small isolated or clustered nodular or wart-like growths, which are strictly superficial
    - Large sessile, or deep nodular mass lesions extending into the dermis or subcutis
- The histologic appearance of both sarcoid and bovine fibropapilloma is characterized by a close association between proliferative disease in the stroma and the epidermis
  - The stromal proliferation resembles a spindle cell sarcoma and, in invasive disease, can extend deep into the subcutaneous connective tissue
  - At the dermal-epidermal junction the stromal proliferation abuts the epidermis and there is exaggerated epithelial down-growth, forming characteristic angular spikes pointing into the adjacent region of stromal proliferation
  - The treatment of equine sarcoid may involve surgery, cryotherapy, immunotherapy, laser, radiation or combination therapy
    - Surgical excision alone is associated with very high recurrence rates
    - The response to treatment is unpredictable
    - Management of periocular tumors is complicated by anatomic considerations

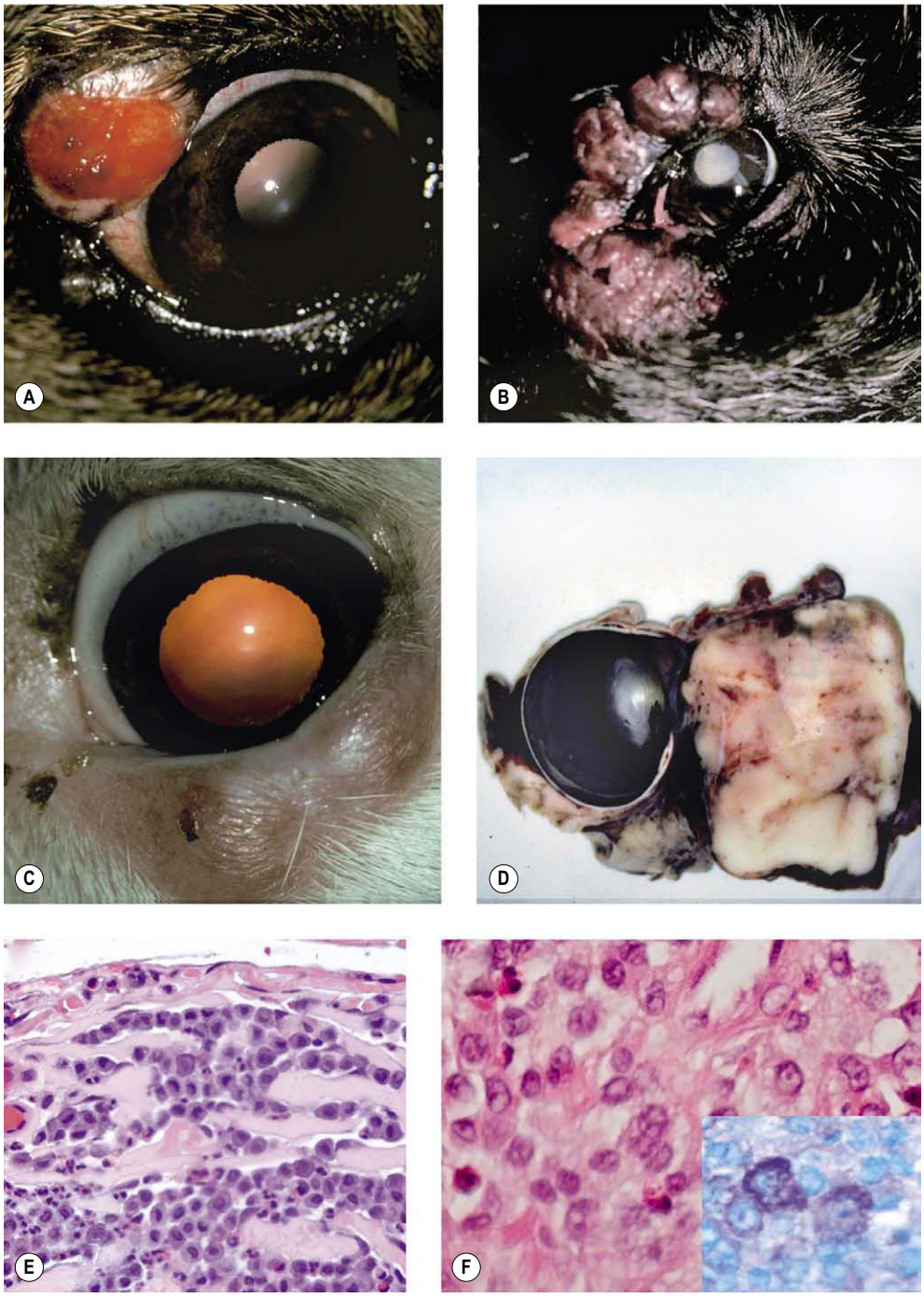


Figure 7.19 Canine mast cell tumor. (A) Mixed Breed, 10 years old: the mass involved the superior lid and palpebral conjunctiva. (B) Mixed Breed, 6 years old: this extensive mass involved the medial canthus and nasal half of the upper and lower lids. The dog also has a mature cataract. (C) English Setter, 11 years old: two elevated areas are present on the lower lid associated with erosion and alopecia of the overlying skin. (D) Mixed Breed, 12 years old: in this dissected specimen, the globe and lids could not be visualized on presentation due to a large firm ulcerative mass. The tumor originated from the superior lid. (E) Photomicrograph of a grade I mast cell tumor showing well-differentiated mast cells nestled between preexisting collagen bundles. (F) Photomicrograph of a grade III mast cell tumor with poorly-differentiated mast cells. The inset is a toluidine blue stain showing small numbers of metachromatic granules in the neoplastic mast cells.

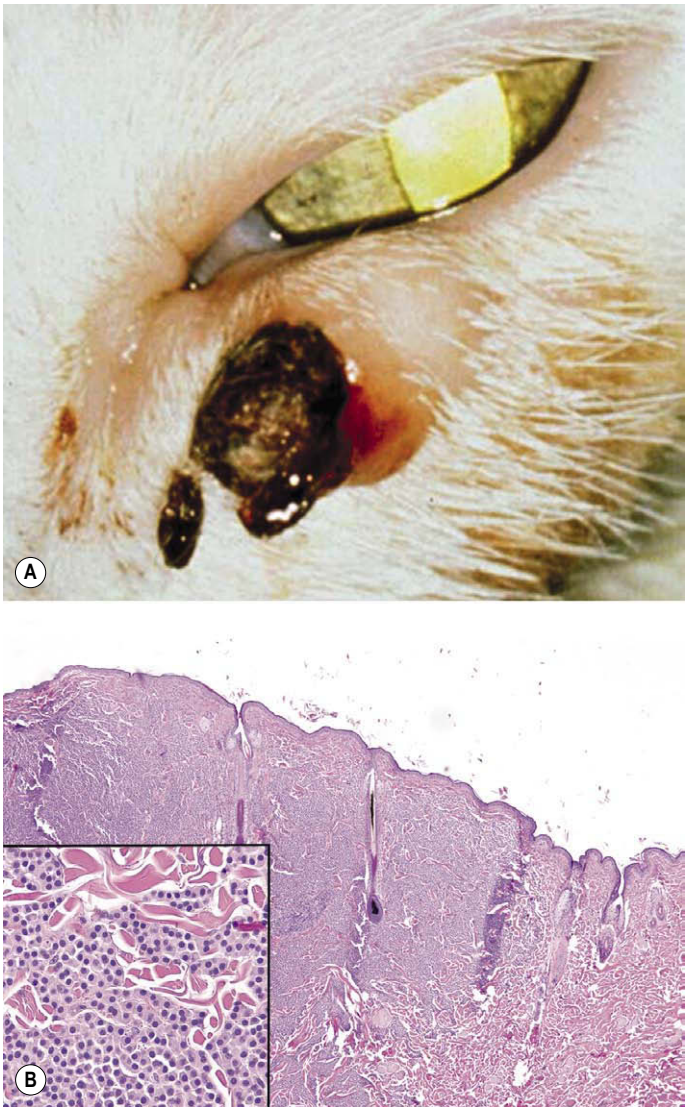


Figure 7.20 Feline cutaneous mast cell tumor. (A) DSH, 16 years old: this mass was present for 10 years, when it became hemorrhagic. (B) Photomicrograph showing well-differentiated neoplastic mast cells filling the space between preexisting dermal collagen and follicles. Higher magnification (inset) showing the bland morphology and monomorphic features which are typical.

Comparative Comments

Tumors of the lid epithelium in humans are common and can be divided into three main groups: benign, precancerous, and malignant. These are in fact a microcosm of the epithelial tumors that occur elsewhere on the human skin.

1. Benign lesions of the eyelid in humans include:
   - Cutaneous horns
   - Papillomas
   - Seborrheic keratoses
   - Inverted follicular keratoses
   - Pseudoepitheliomatous hyperplasia
   - Keratoacanthoma
   - Large cell acanthomas.
2. Non-melanocytic pre-cancerous lesions of the human eyelid include:
   - Actinic keratoses
   - Carcinoma *in situ*
   - Radiation dermatosis
   - Xeroderma pigmentosum.
3. The major epithelial malignancies of the human lid are basal cell carcinoma and squamous cell carcinoma:
   - Basal cell carcinoma is a tumor of the basal cells, located at base of the epidermis
     - It is the most common malignancy of the eyelids and accounts for approximately 90% of all malignant tumors of the lid and 20% of all lid tumors in humans
   - Squamous cell carcinoma (SCC) constitutes less than 5% of epithelial neoplasms of the human eyelid
     - SCC in humans typically arises in sun-damaged skin in elderly, fair-skinned individuals
   - Sebaceous gland carcinoma is the most significant of the many malignant tumors arising from the adnexal structures of the lid
     - This is the second most common malignancy of the eyelids in humans, and occurs most commonly in elderly women and in Asians
     - The preferred sites of involvement are the upper lid, brow, and caruncle
     - Sebaceous gland carcinoma is often clinically misdiagnosed as unilateral blepharoconjunctivitis or recurring chalazion
     - This is an aggressive tumor that commonly exhibits local extension, as well as lymphatic and hematogenous spread
     - The finding of intracytoplasmic lipid in the tumor cells is essential for diagnosis.

EYELID MARGIN MASSES

Canine meibomian gland adenoma/ epithelioma (Fig. 7.24)

Meibomian adenoma and epithelioma represent 10% of tumor submissions to COPLOW. This is probably a gross under-estimate of the frequency of this tumor, since small masses are likely to either not be submitted when excised; treated in such a way that the tissue is destroyed, or submitted to a general rather than ophthalmic pathology laboratory.

- Benign meibomian gland tumors present as focal or multifocal nodular masses which are often exophytic and papillary
- They may cause problems related to their contact with the corneal surface causing irritation, or may be considered a cosmetic problem
- Meibomian gland adenoma
  - Most of the tumor is made up of fully differentiated meibomian glandular tissue:
    - Holocrine secretory cells
    - Keratinizing ducts
  - As a general rule: adenoma is smaller, more superficial, and more likely to be exophytic than epithelioma
- Meibomian gland epithelioma
  - Most of the tumor is made up of undifferentiated basal cells with rare sebaceous or squamous differentiation
  - Epitheliomas are more likely to be pigmented
  - Epitheliomas are slightly larger and more likely to be deeper in the lid margin dermis than adenomas

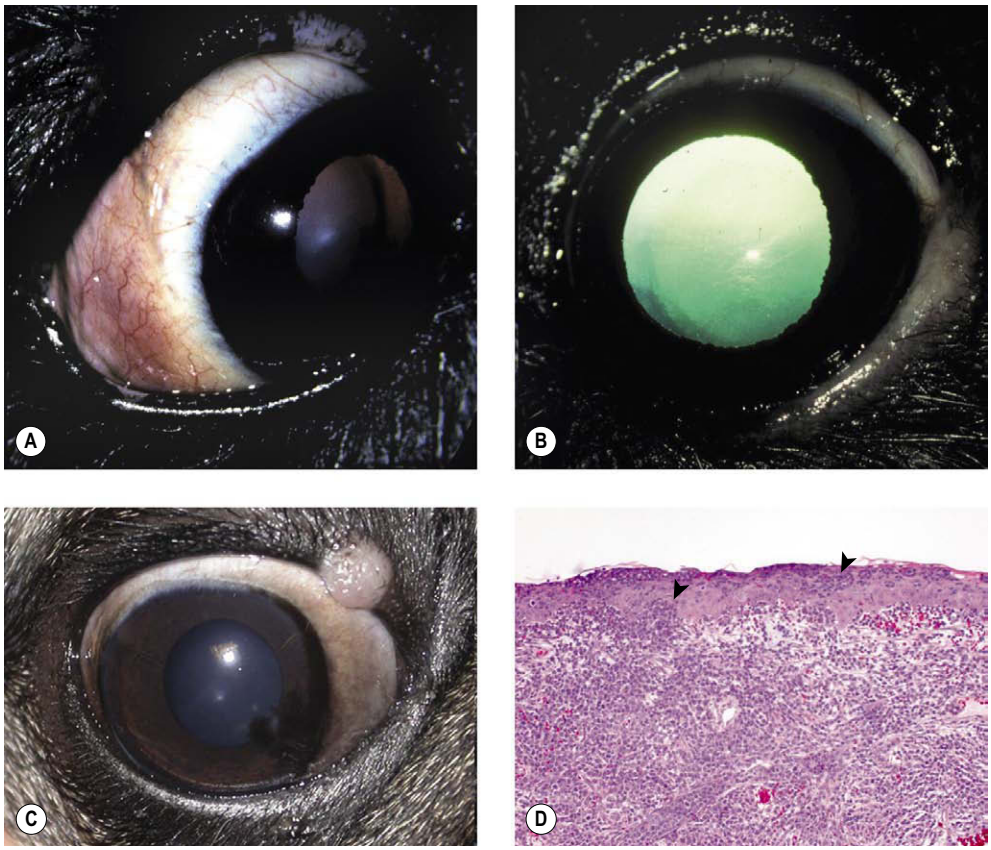


Figure 7.21 Epitheliotropic lymphoma. (A) Miniature Schnauzer, 11 years old: the hyperemic, elevated conjunctival lesion developed at the same time as the lid lesion in (B). (B) The lower lid is thickened and depigmented. The diagnosis of epitheliotropic lymphoma, was confirmed by a biopsy of the lower lid in this left eye of the same dog as (A). (C) A focal exophytic skin mass was seen on a dog with epitheliotropic lymphoma, mycosis fungoides. (D) Photomicrograph of the epidermis from the same dog as (C) showing aggregates of neoplastic cells within defined cavities in the epidermis (arrows) and also within the dermal connective tissue.

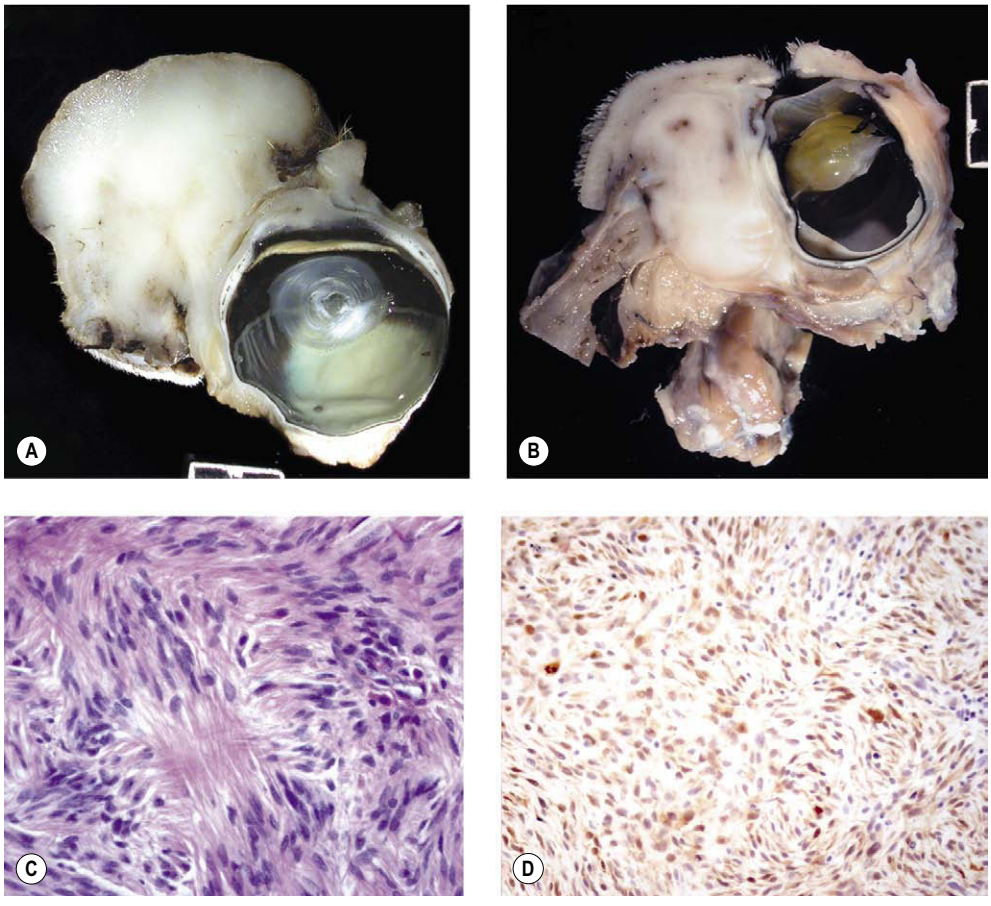


Figure 7.22 Peripheral nerve sheath tumors of the feline eyelid/schwannoma. (A,B) Gross photographs showing poorly-defined mass lesions infiltrating, effacing and distorting the connective tissue of the eyelid. (C) Photomicrograph showing neoplastic spindle cells arranged such that the nuclei form rows and cords, Antoni A pattern. (D) Immunohistochemistry stains positive for S-100 protein.

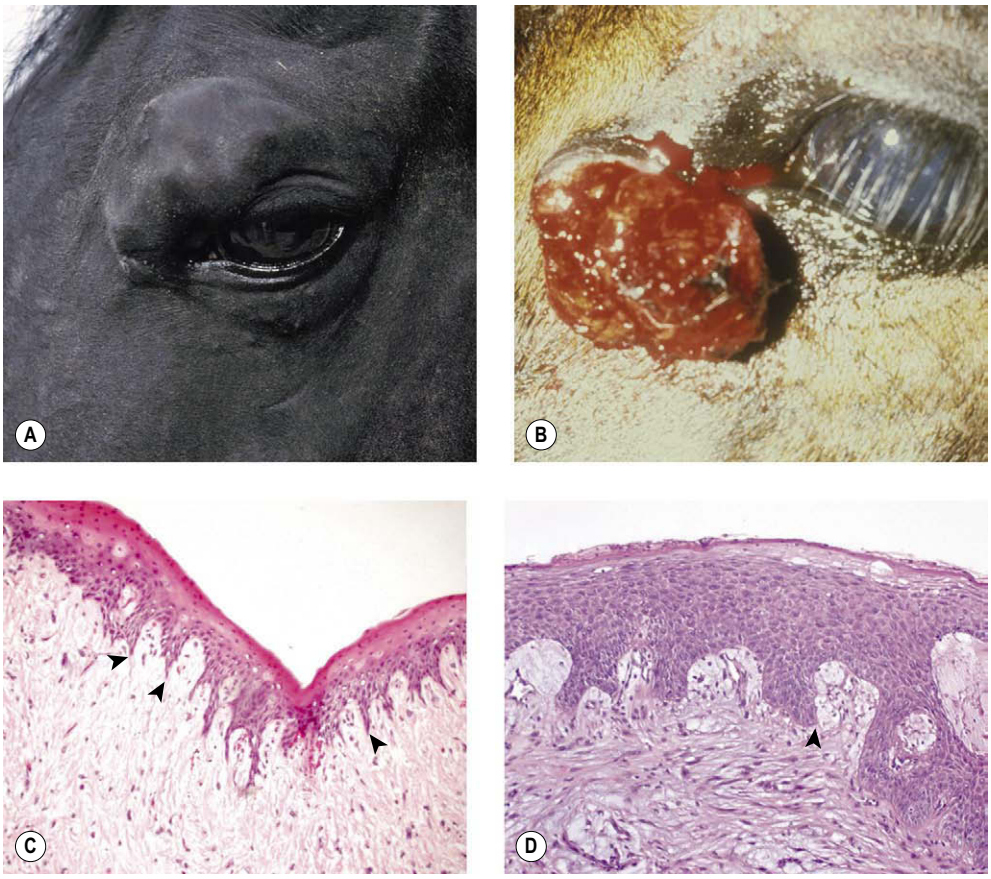


Figure 7.23 Equine sarcoid. (A) Thoroughbred, 5 years old: the large, firm, nonulcerated mass was tightly adherent to underlying tissue. (B) Mule, 7 years old: this nodular skin tumor was severely ulcerated, with superficial necrosis. (C,D) Photomicrographs showing the typical relationship between the epidermis and the neoplastic stromal tissue in equine sarcoid. The epidermis interdigitates with the neoplastic spindle cells via angular epithelial pegs (arrows) that extend deeply into the stroma.

- Lipogranuloma surrounding adenoma or epithelioma (Fig. 7.25)
  - Either variant of the benign meibomian gland tumors is likely to be surrounded by a variably sized lipogranuloma with:
    - Epithelioid macrophage cells
    - Multi-nucleated cells
    - Large, empty 'lipid lakes'
  - Linear, birefringent material within the cytoplasm of the macrophage cells
    - Forms complex membranous electron-dense material in the cytoplasm of the macrophage cells
    - Birefringent material is not seen in lipogranuloma surrounding canine cutaneous sebaceous gland tumors.

Canine meibomian gland adenocarcinoma

There are only three examples of this tumor in the COPLOW archive.

- This is a rare, malignant variant of the meibomian gland tumor
- The tumor is characterized by anaplastic cellular features, rare meibomian gland secretory features and local invasion.

Lid margin melanocytic tumors (melanocytoma) (Fig. 7.26)

There are 52 cases in the COPLOW collection (0.9% of tumor submissions). The reader is referred to the section above on melanocytic tumors of the haired eyelid skin

- Multifocal eyelid margin melanocytomas are seen in Vizslas, and in Doberman Pinschers, particularly those with the so-called white color-dilute coat color (Fig. 7.27).

Lipogranuloma (chalazion) (Fig. 7.28)

- As mentioned above, lipogranuloma formation is common surrounding benign tumors of meibomian gland origin. However, lipogranulomata can form a nodular mass lesion in isolation, without a co-existing meibomian gland tumor
  - White nodular mass at the lid margin
  - Histologically the lipogranuloma surrounds the non-neoplastic meibomian gland
  - It is postulated that the granuloma reflects a reaction to release of meibomian lipid within the tissues
  - As with the lipogranuloma that surrounds adenoma, there is often linear birefringent material in the cytoplasm of macrophage cells in lipogranulomas surrounding meibomian glands.

Squamous cell carcinoma of the lid margin in cats (multifocal squamous cell carcinoma) (Figs 7.29, 7.30)

There are 10 cases of multifocal squamous cell carcinoma involving the lid margin in the COPLOW collection.

- Squamous cell carcinoma in cats, when it involves the lid margins, usually also extends into the haired skin and is part of

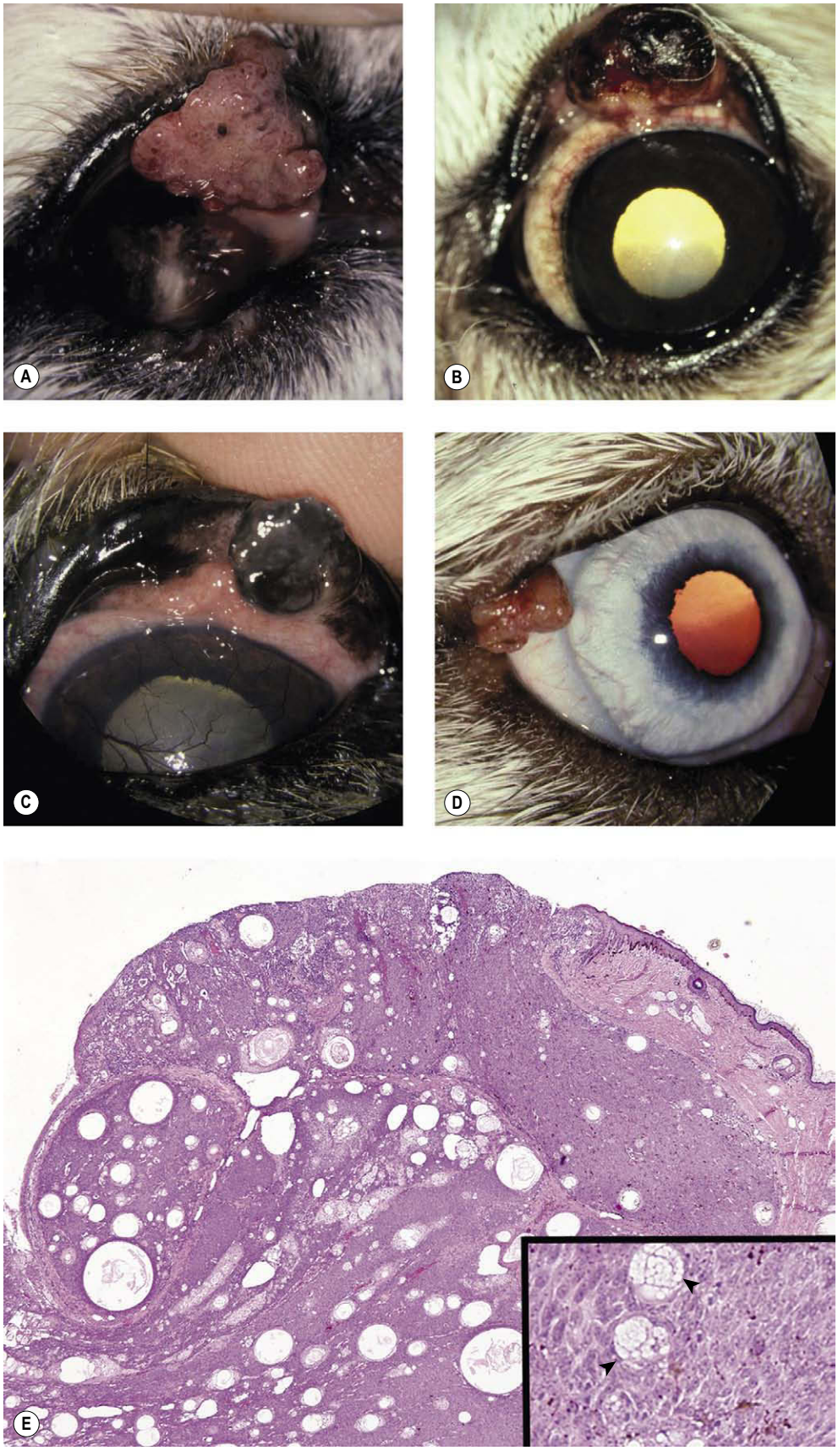


Figure 7.24 Canine meibomian gland adenoma and epithelioma. (A) Cocker Spaniel, 12 years old: a non-pigmented cerebriform mass involved the lid margin and palpebral conjunctiva. (B) Cocker Spaniel, 10 years old: this mass had a hemorrhagic surface. (C) Shih Tzu, 9 years old: the pigmented mass involved the lid margin and palpebral conjunctival surface. (D) Siberian Husky, 6 years old: the exophytic hyperemic mass involves the lid margin and palpebral conjunctival surface. (E) Photomicrograph showing a meibomian epithelioma characterized by sheets of poorly-differentiated basal cells. Inset: occasional cells show sebaceous differentiation (arrows). There are also scattered melanocytes.

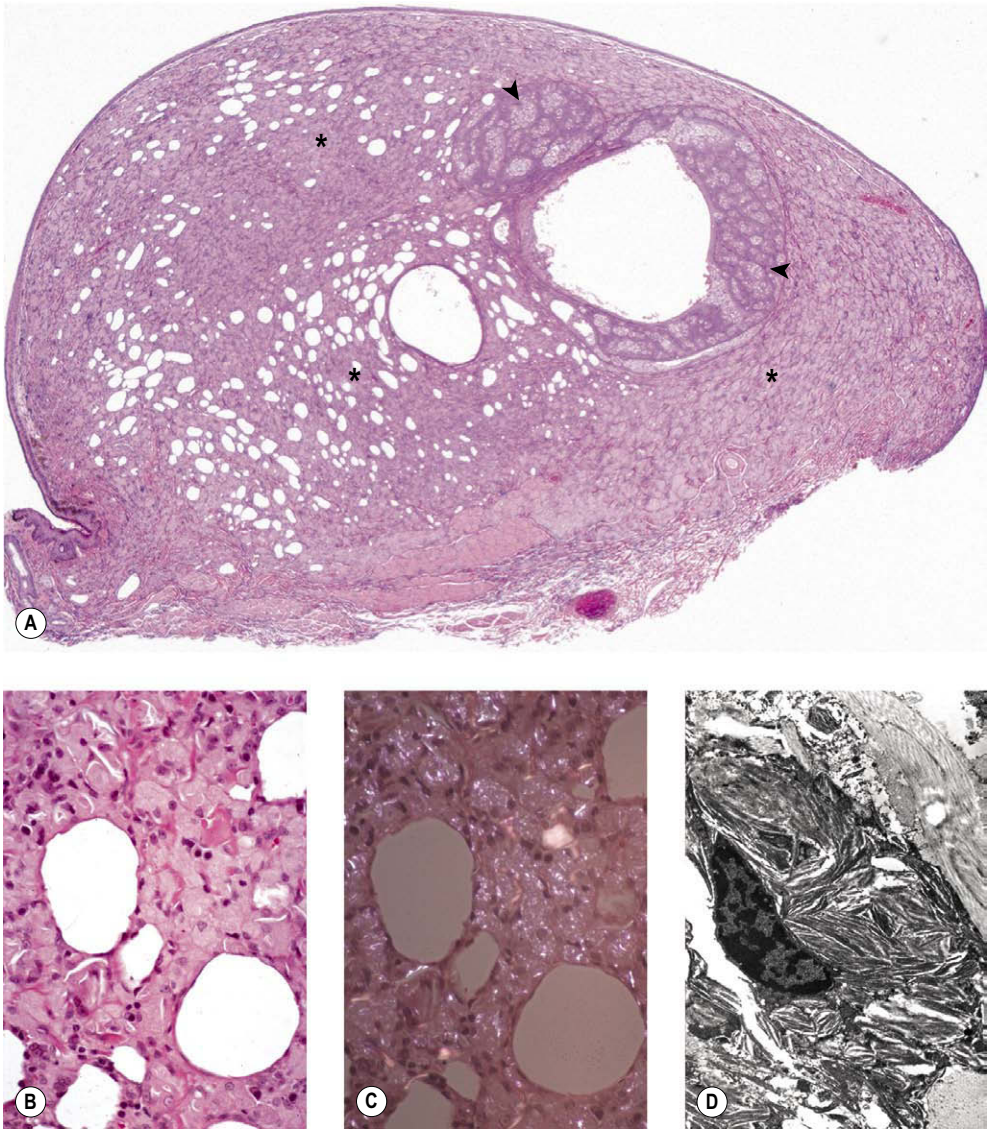


Figure 7.25 Canine meibomian gland adenoma with lipogranuloma. (A) Low magnification photomicrograph of the lid margin of a dog showing a small meibomian gland adenoma (arrows) surrounded and dwarfed by a much larger lipogranuloma (*) reacting to released meibomian gland secretions. (B,C) Higher magnification showing macrophage cells containing birefringent linear material (C) when viewed with intense polarized light. About half of the lipogranulomas surrounding meibomian glands or meibomian tumors in dogs have birefringent material in the cytoplasm. (D) Transmission electron micrograph showing phagocytes with birefringent material reveals complex linear membranous material in the cytoplasm.

a complex of dysplastic epithelium with multicentric squamous cell carcinoma

- There is often diffuse conjunctival disease with multifocal areas of epithelial dysplasia but not necessarily neoplasia. A similar situation exists in the horse, but in that species the neoplasm commonly involves conjunctival tissue and will, therefore, be addressed in the next section.
- Careful evaluation of the margins of the neoplasm in the haired skin of the eyelid reveals disorganized and dysplastic epithelium, often most easily identified in the follicular epithelium.

Squamous cell carcinoma of the lid margin in dogs (Fig. 7.31)

There are only three canine cases of lid margin squamous cell carcinoma in the COPLOW collection.

Squamous cell carcinoma of the lid margin in horses and cattle

- This is a very common clinical presentation, particularly in breeds that lack periocular pigmentation
- As described above for cats, squamous cell carcinoma of the lid margin in horses and cattle generally shows extensive conjunctival involvement and is therefore considered later in this chapter, as a conjunctival neoplasm.

Mesenchymal hamartomas of the lateral canthus (Fig. 7.32)

There are seven of these tumors in the COPLOW collection, six of which involved the temporal orbital rim.

- A hamartoma is a mass lesion associated with fully differentiated, non-neoplastic tissue, appropriate to the location of the mass

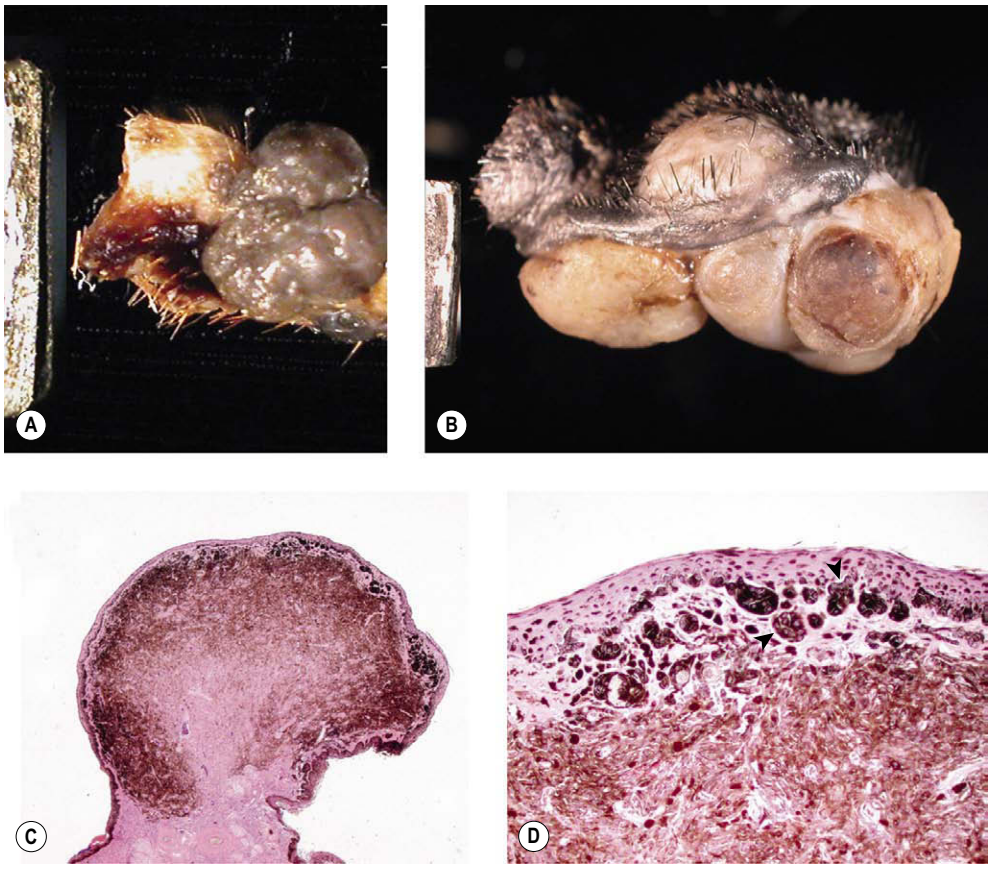


Figure 7.26 Lid margin melanocytoma. (A,B) Gross photographs showing lid margin melanocytomas in submitted specimens. (C,D) Photomicrographs showing variably pigmented neoplastic masses abutting and within the epidermis (arrows).

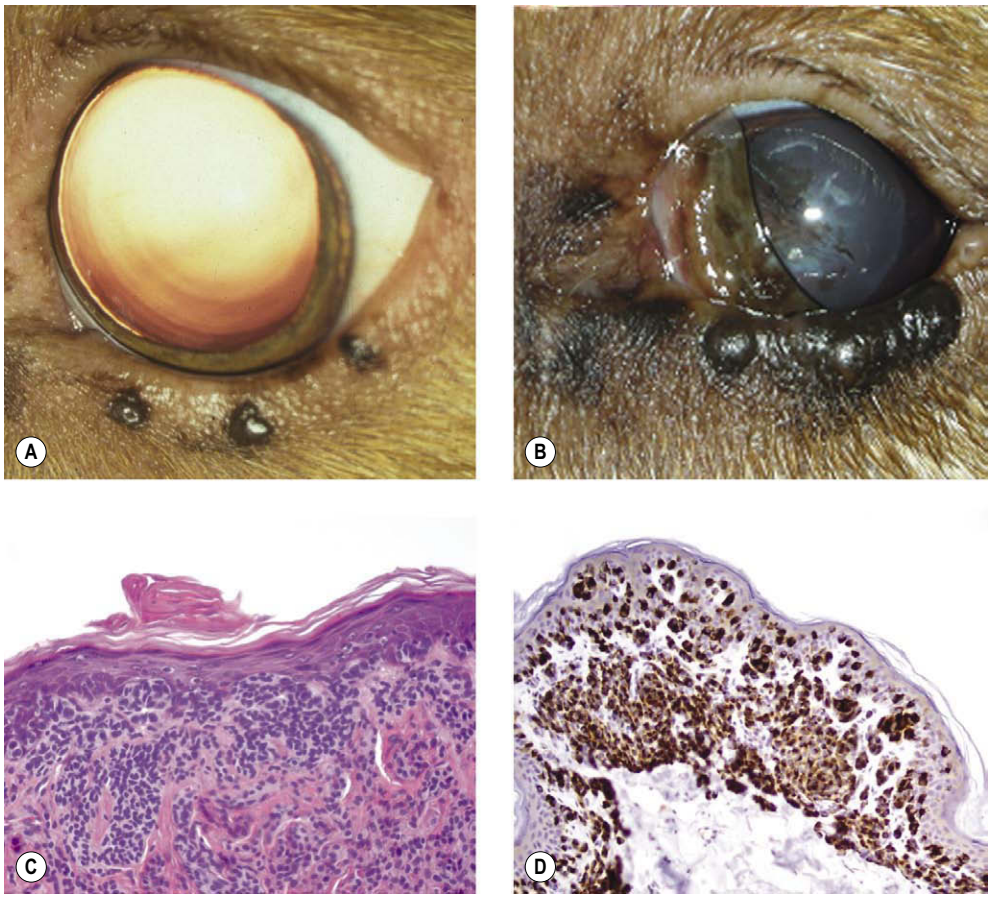


Figure 7.27 Multifocal melanocytoma. (A) Nova Scotia Duck Tolling Retriever, 8 years old: the bilateral condition consisted of multifocal pigmented elevated tumors and diffuse areas of dermal pigmentation. (B) Vizsla, 10 years old: there is diffuse cutaneous pigmentation with multifocal raised masses predominantly in the lower eyelid. (C) Photomicrographs showing multifocal melanocytoma in a white Doberman Pinscher. Proliferating melanocytes resemble human nevus cells. (D) The neoplastic melanocytes stain positive for Melan-A with immunohistochemistry.

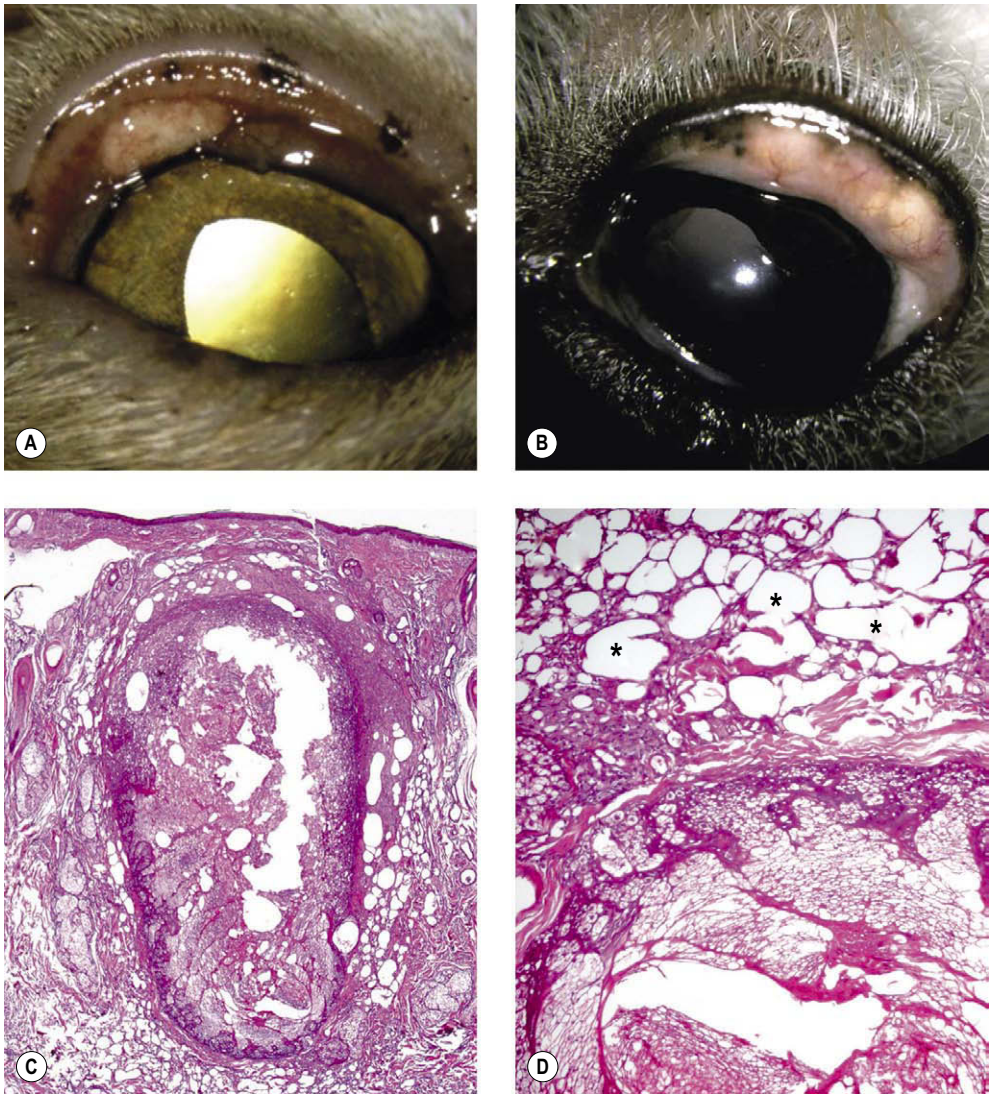


Figure 7.28 Chalazion. (A) DSH, 5 years old: the yellowish subepithelial nodule is present on the superior palpebral conjunctiva in the area of the superior meibomian glands. (B) Poodle, 6 years old: two-thirds of the superior meibomian glands are involved. (C,D) Inflammation within and surrounding diseased meibomian glands in chalazion. Lipid lakes (*) occur within lipogranulomatous inflammation.

- Mesenchymal hamartomas, composed of collagenous connective tissue, adipose tissue and, usually, skeletal muscle tissue, are occasionally removed from the orbital rim in dogs.

CONJUNCTIVITIS

General philosophy on the pathology of conjunctivitis

- Small conjunctival biopsies are often submitted in the hope that the morphology will reveal a cause of inflammatory disease. Unfortunately, there are seldom morphologic features that suggest a specific diagnosis
- In COPLOW submissions, the diagnosis of conjunctivitis is generally made by describing the kind of inflammatory exudates and/or infiltrates seen
- If there is an apparent increase in the relative number of mast cells, the suggestion is made that conjunctivitis might be related to hypersensitivity.

Comparative Comments

The opportunity to study conjunctival pathology in humans usually occurs in the following instances:

- A biopsy specimen, from an inflammatory, degenerative, or neoplastic process. These may either be excisional or partial biopsies
- Conjunctival scrapings, e.g., in the diagnosis of trachoma
- Impression cytology, in which surface cells have been removed and are stained for recognition of malignant cells, inclusions, or other abnormalities for exenteration specimens submitted following the removal of advanced malignant processes.

In the organization and teaching of human conjunctival pathology, the following categories are usually considered:

- Congenital and developmental anomalies
- Inflammations and infections
- Degenerations
- Systemic diseases
- Tumors.

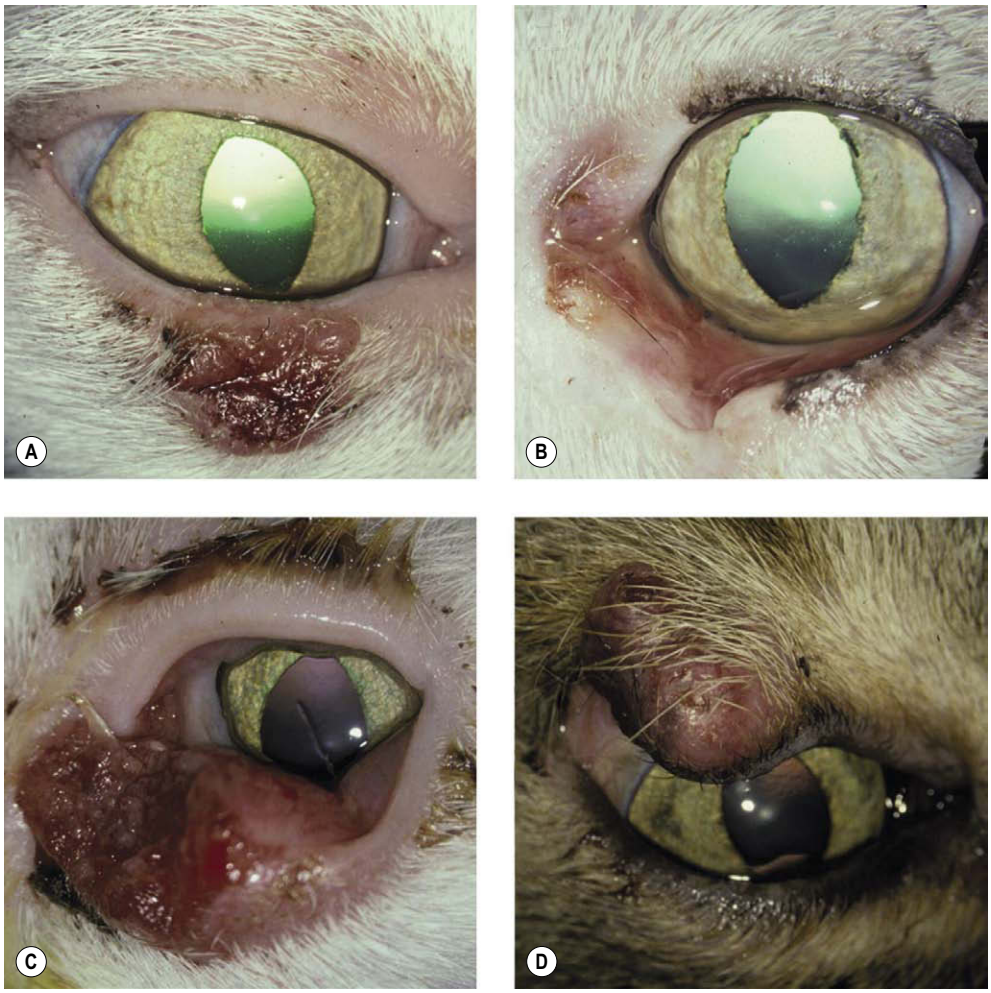


Figure 7.29 Feline eyelid margin squamous cell carcinoma, clinical. (A) DSH, 5 years old: this erosive lesion has not yet involved the free lid margin. (B) DSH, 7 years old: the free lid margins, lower lid and medial canthus are involved in this case. (C) DSH, 17 years old: the tumor is elevated and erosive. The nictitans and palpebral conjunctiva are also involved. (D) DSH, 8 years old: the tumor has disfigured the superior lid and extended into the superior palpebral conjunctiva.

Comparative Comments (continued)

Within these categories are encompassed many of the entities described in this chapter in various other species, such as pseudopterygia, pterygia, non-specific chronic conjunctivitis, ligneous conjunctivitis, fibrous histiocytoma, herpes virus infection, lipogranulomas, granulomas associated with injection sites, and onchocerciasis.

The frequency and specific appearance of these lesions in man appear to vary in many instances from that described in other species.

Pseudopterygium in rabbits (Fig. 7.33)

- This is an idiopathic disease of the conjunctiva in rabbits, which has the following characteristic features:
  - The disease is often unilateral, although some rabbits show bilateral ocular involvement
  - Signs of pain, irritation or inflammation are minimal or absent
  - The hallmark of the disease is a circumferential inward folding of the bulbar conjunctiva, thus closing over the clear cornea like a purse-string. The condition has also been termed 'epicorneal conjunctival membrane'
    - In contrast to pterygium in humans, the space between the conjunctival fold and the corneal surface is only rarely interrupted by an adhesion
    - The axial opening in the conjunctival fold is always circular, and has smooth margins
  - Surgical debridement of the base of the conjunctival fold results in re-growth
  - Histopathology
    - Minimal inflammation or edema
    - The stroma is generally the typical loose connective tissue of the conjunctival substantia propria
    - Rarely, at the axial, migrating margin, contractile cells rich in actin may be observed, that are morphologically similar to smooth muscle cells.

Ligneous conjunctivitis in dogs (Figs 7.34, 7.35)

There are six cases of ligneous conjunctivitis, four in Doberman Pinschers and two in littermate Golden Retrievers, in the COPLOW collection (Fig. 7.35).

- This is a rare condition. Ligneous conjunctivitis has been reported as an entity only in Doberman pinschers and Golden retrievers
- Clinically, the condition presents as a bilateral ulcerative conjunctivitis, with an adherent dense pseudomembranous exudate
- In some cases, there are oral mucosal lesions of similar appearance

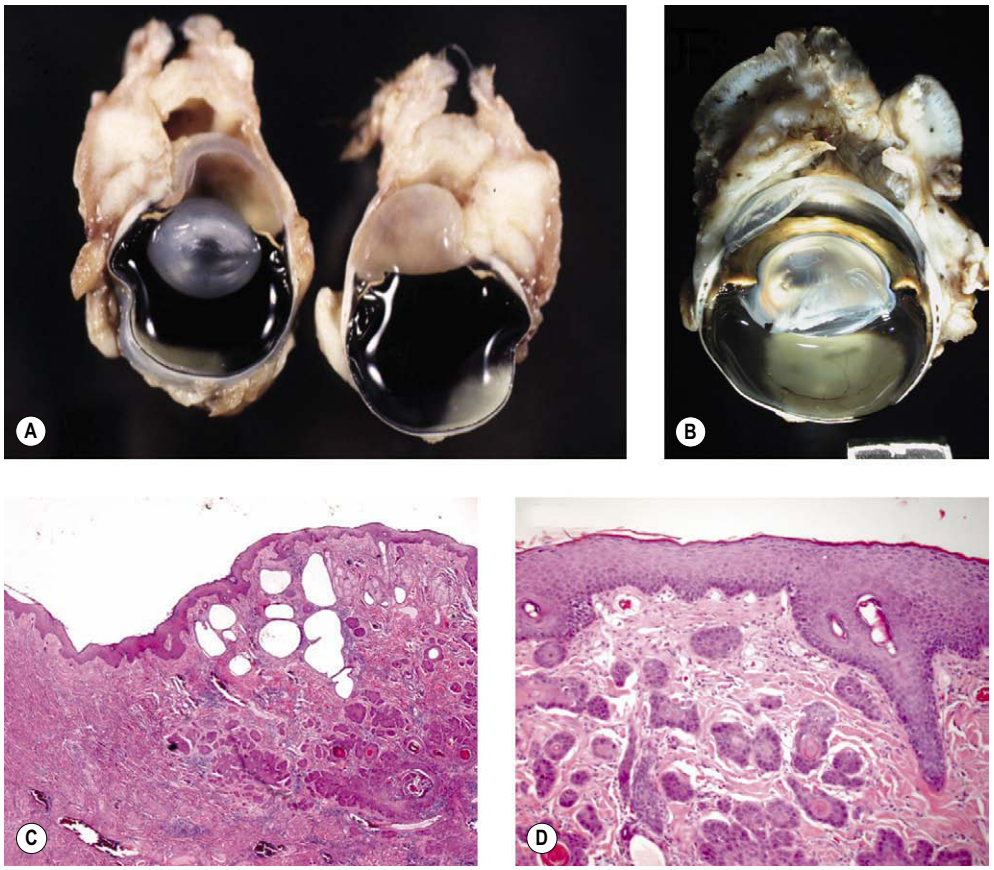


Figure 7.30 Feline eyelid margin squamous cell carcinoma, pathology. (A,B) Gross photographs showing globes and lids from cats with lid margin squamous cell carcinoma invading and effacing surrounding tissues. (C,D) Photomicrographs showing invasive neoplastic squamous epithelium surrounded by a desmoplastic stromal response.

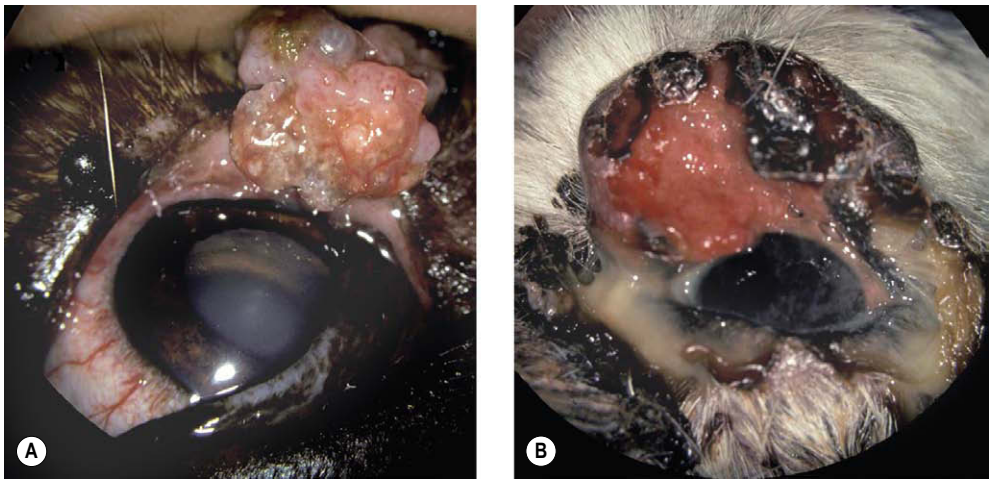


Figure 7.31 Canine eyelid margin squamous cell carcinoma. (A) Mixed Breed, 8 years old: this proliferative tumor first involved the superior lids and palpebral conjunctiva. (B) Cocker Spaniel, 12 years old: the entire superior lid, palpebral conjunctiva and medial canthus were involved with this proliferative hyperemic mass.

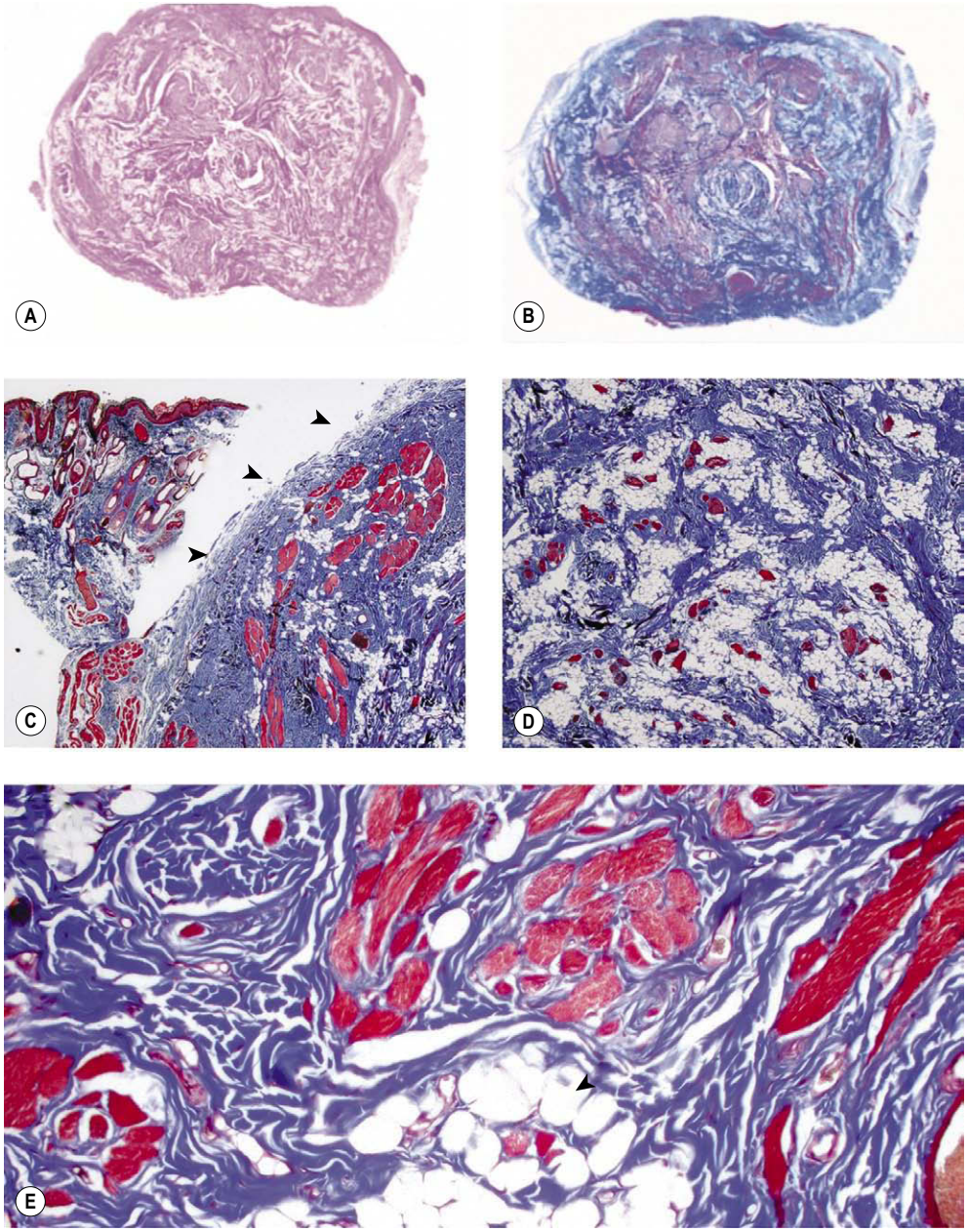


Figure 7.32 Mesenchymal hamartoma. (A,B) Low magnification photomicrographs of mesenchymal hamartomas, from canine orbital rims, stained with H&E (A) and trichrome (B). (C) Photomicrograph showing the margins of the mass lesion (arrows) (Trichrome stain). (D) Low magnification photomicrograph showing the relationship between collagen (blue) adipose tissue (white) and muscle (red) (Trichrome stain). (E) Higher magnifications showing that the mass is composed of fully-differentiated collagenous connective tissue (blue), adipose tissue (arrow) and skeletal muscle (red) (Trichrome stain).

- The characteristic clinical feature is the hard and rigid 'wooden' consistency of the affected tissue
- There is a reported link to renal glomerular disease, and to respiratory disease in affected dogs.
- Morphologic characteristics:
  - Ulcerative lesions
  - Hyaline, cell-poor matrix with epithelial elements buried deeply within this matrix
    - Fails to stain for amyloid
    - Stains bright red with trichrome stain, and does not demonstrate birefringence with polarized light
  - In humans there is a condition, also called ligneous conjunctivitis, which has a very similar morphologic appearance
    - The human disease is thought to be linked to plasminogen deficiency
    - This link has been reported in one Golden retriever but has not been definitively established in other affected dogs.

Episcleritis and canine nodular granulomatous episclerokeratitis (NGE, fibrous histiocytoma, nodular fasciitis) (Figs 7.36, 7.37)

There are 234 cases of NGE in the COPLOW collection. Although in clinical practice, Collie dogs are over-represented, this is not the case

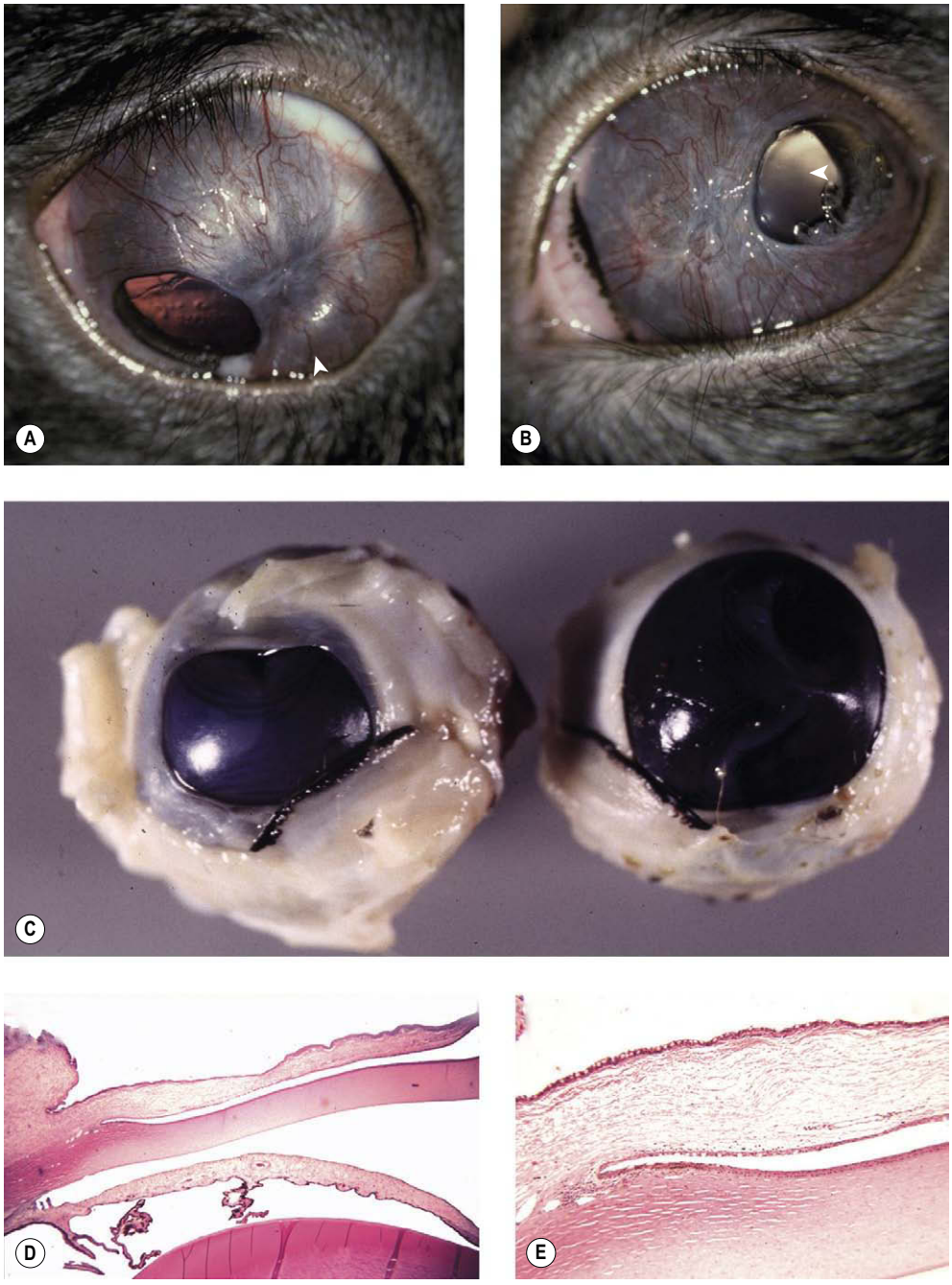


Figure 7.33 Pseudopterygium in rabbits. (A) Dwarf Lop-Eared Rabbit: the conjunctival overgrowth from the limbus has resulted in a small paracentral aperture through which the pupil is just visible and a cyst-like structure (arrow). (B) The left eye in the same rabbit as (A) better demonstrates the small axial area of clear cornea (arrow). (C) Gross photograph showing an affected eye and an unaffected eye from a rabbit. (D,E) Lower and higher magnification photomicrographs showing the fold of near normal conjunctival epithelium and connective tissue extending as a flap from the limbus.

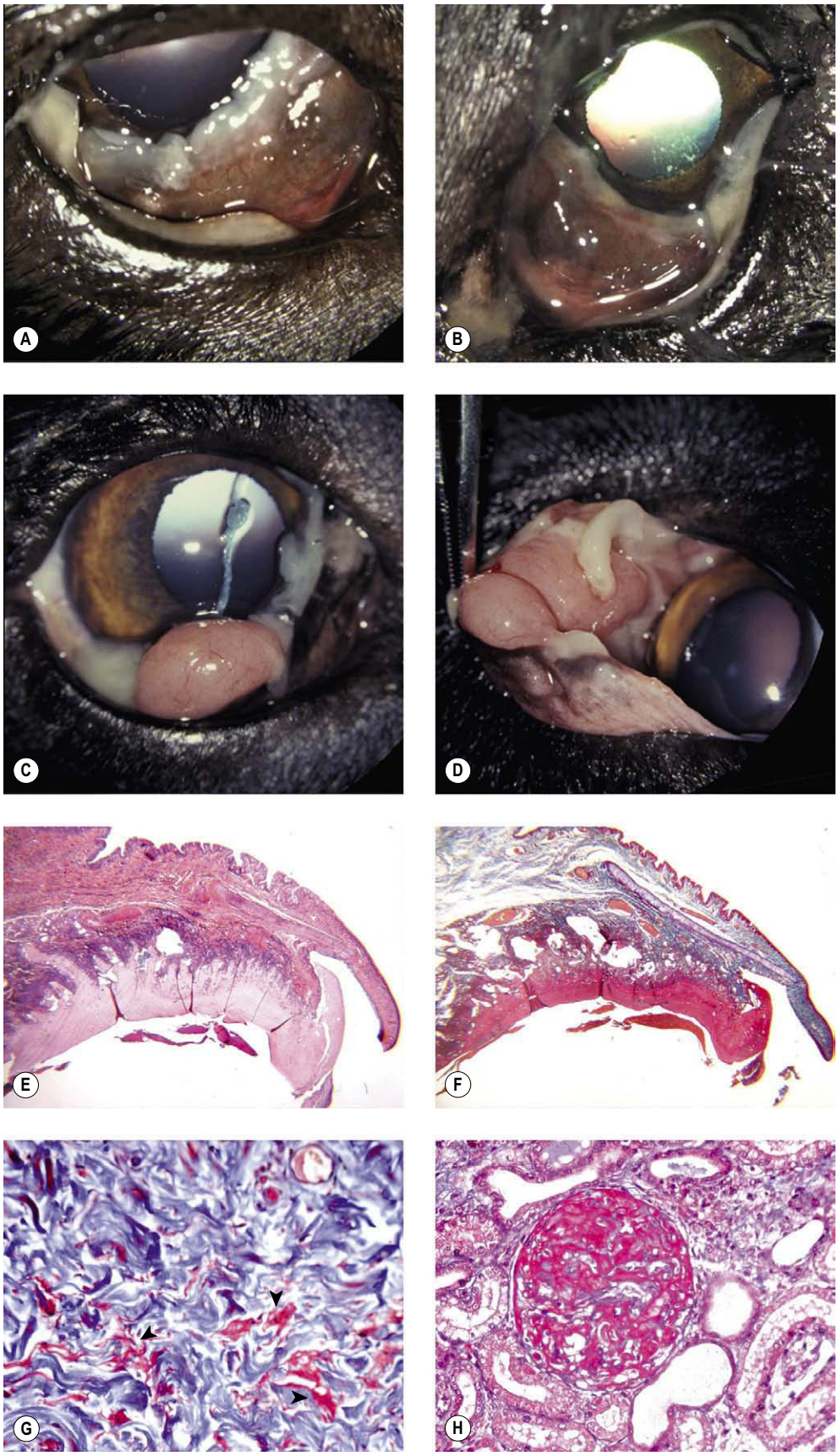


Figure 7.34 Ligneous conjunctivitis. (A) Doberman Pinscher, 5.5 years old: a thick firm gray membrane is tightly adhered to the free-lid margin of the nictitans and inferior palpebral conjunctiva of the lower lid. (B) Left eye of the dog in (A) showing the severely hyperemic nictitans with the gray membrane. (C) Doberman Pinscher, 6.5 years old: this individual is similar to the previous case, but also has firm elevated conjunctival lesions. (D) Left eye of the dog in (C) with the nictitans everted, showing large conjunctival swellings. (E,F) Low magnification photomicrographs showing hyaline protein, typical of ligneous conjunctivitis, deposited in the subepithelial stroma of the bulbar aspect of the third eyelid (E, stained with H&E; F, trichrome). The hyaline protein stains bright red with trichrome (F). (G) High magnification of a trichrome stained conjunctiva showing remnants of red-staining ligneous material away from the main deposit (arrows). (H) Photomicrograph showing similar ligneous material distorting the structure of the renal glomerulus.

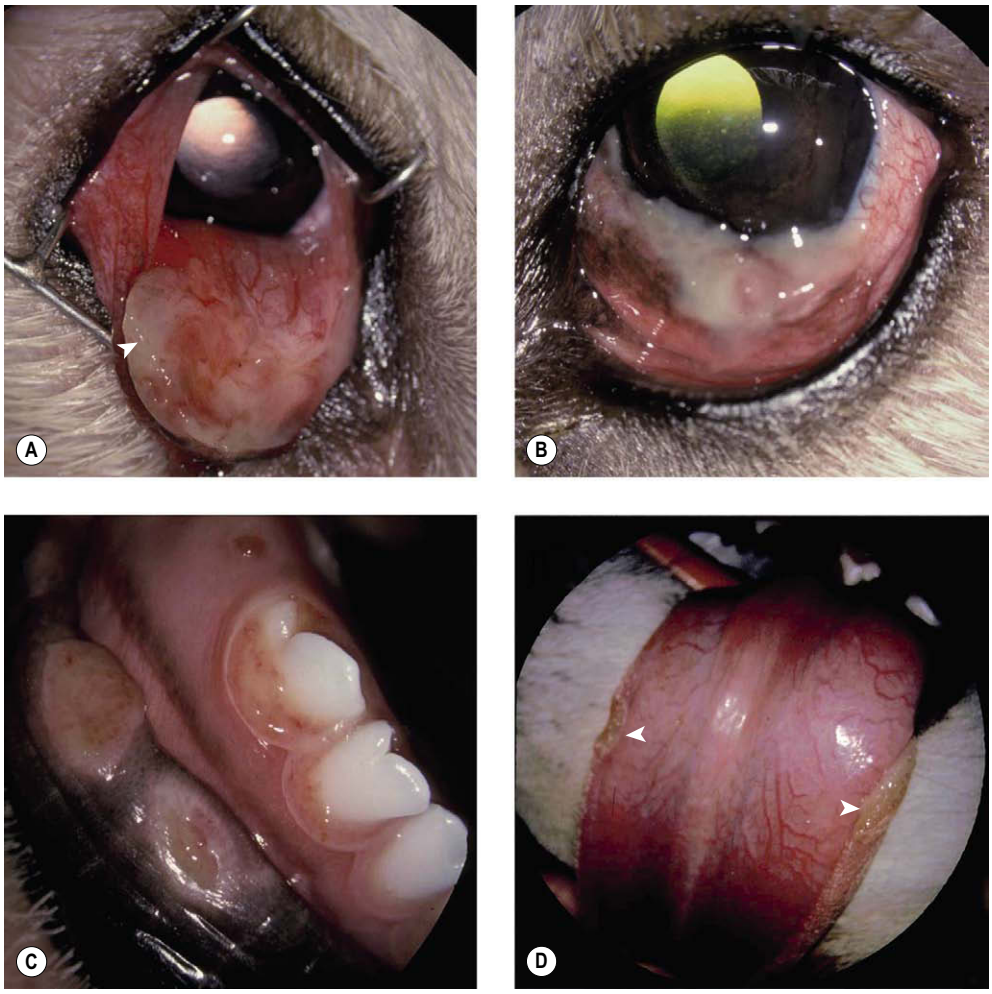


Figure 7.35 Ligneous conjunctivitis in a Golden Retriever. (A) Golden Retriever, 4.5 months old: this dog and one littermate were similarly affected. The thick gray membrane can be seen at the junction of the conjunctiva and skin on the lower lid (arrow). (B) The left eye of the dog in (A) showing a similar membrane and mucous on the margin of the nictitans. (C) The same dog had erosive lesions on the lower lip and the gingiva. (D) This dog's tongue had two erosive lesions (arrows).

in the COPLOW collection. The COPLOW collection has only 14 cases in Collies out of the 234 total cases.

- This is an idiopathic, inflammatory disease of the conjunctival substantia propria and/or episcleral tissue in dogs. Lesions may occur anywhere on the episclera and conjunctiva
- Rather than a single, well-defined, clinical and histological entity, this represents a broad spectrum of episcleral inflammatory disease
  - Clinical presentation ranges from relatively diffuse sub-conjunctival thickening (episcleritis) to well-defined, firm nodules (NGE)
  - Relative numbers of different inflammatory cell types and presence and extent of fibroblast proliferation and collagen deposition are highly variable
- Collie dogs are reported to have a predisposition to the development of nodular granulomatous episcleritis NGE (but, see above)
  - This may be a reflection of clinicians' ability to recognize very characteristic disease features and response to treatment in this breed, and thus reach a clinical diagnosis without pursuing histologic confirmation
  - Some clinicians refer to this condition as proliferative keratoconjunctivitis in the Collie breed
  - The disease in Collies is relatively aggressive but generally responds well to anti-inflammatory treatment (Fig. 7.38)
- The classic disease is a nodular mass lesion deep to the conjunctival epithelial surface and abutting the sclera at the limbus. However, particularly in Collies, the conjunctiva and tissues of the third eyelid and eyelid may also be involved in the disease process
- The nodular disease often responds to anti-inflammatory treatment or debulking surgery. Therefore, only atypical lesions tend to be sampled and submitted to the pathology laboratory
- Typical morphologic features include:
  - The lesion forms a nodule. There should be a well-defined margin, with adjacent near normal connective tissue
  - The lesion subtends the conjunctival epithelium which is characteristically intact over the mass
  - There is a mixture of lympho-plasmacytic inflammatory cells and larger cells resembling histiocytes, with minimal or no suppurative component. The histiocytic component may include multi-nucleate cells
  - There is often a variable population of spindle cells with or without collagen matrix deposition:
    - Mass lesions which are primarily made up of spindle cells and collagen are diagnosed at COPLOW as NGE- nodular fasciitis variant
  - Nodular granulomatous episcleritis lacks features of classical granulomatous inflammation, with no distinct nodules of epithelioid macrophage cells surrounding a necrotic center

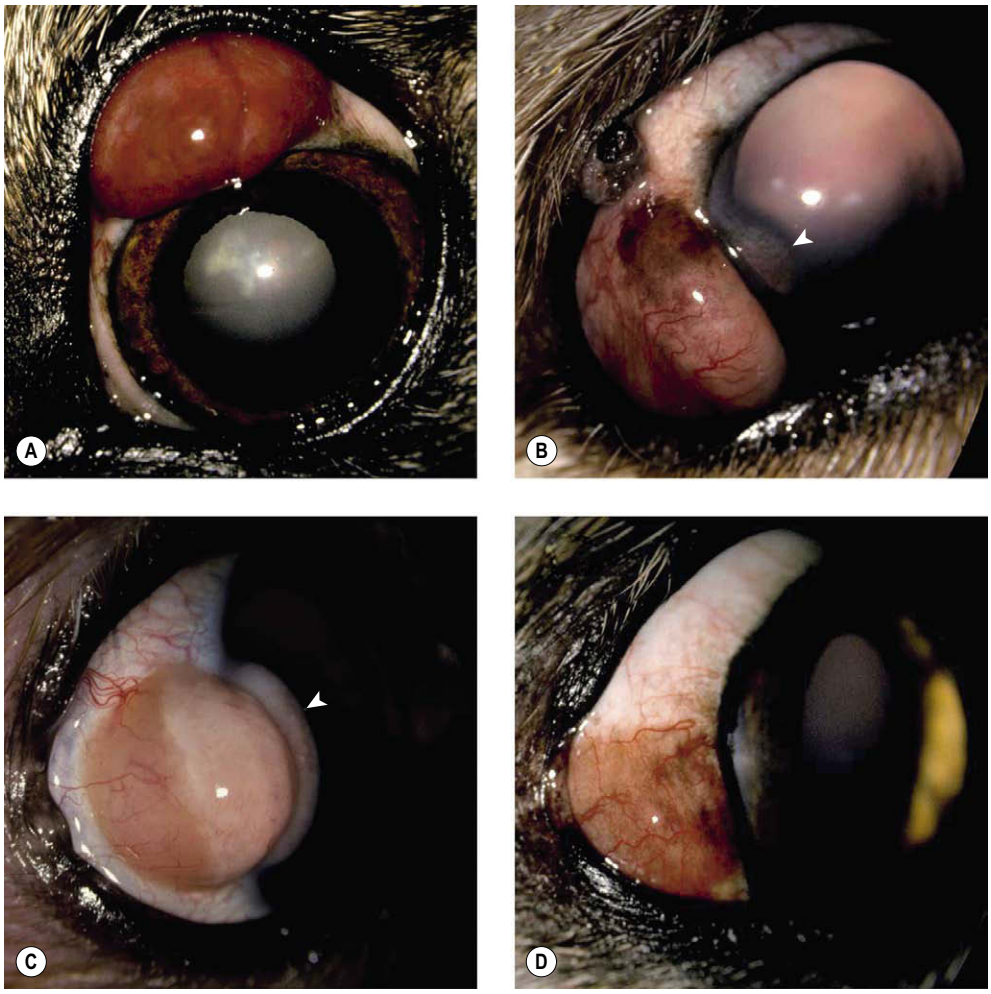


Figure 7.36 Canine nodular granulomatous episcleritis (NGE). (A) Pembroke Welsh Corgi, 14 years old: this firm mass originated in the superior episclera and had not invaded the cornea. (B) Golden Retriever, 9 years old: this pink elevated mass originated from nasal episclera with mild extension into the adjacent cornea (arrow). (C) Shetland Sheepdog, 10 years old: this mass extended into the superficial cornea. Lipid keratopathy (arrow) is present at the leading edge of the lesion. (D) Greyhound, 6 years old: the pink mass originated temporally and did not significantly invade the cornea.

- Recently it has been reported that not all of the large cells are histiocytic, and some may be smooth muscle or myofibroblasts.

Feline herpesvirus keratoconjunctivitis, FHV-1 (Fig. 7.39)

- Feline herpesvirus-1 causes both a primary and secondary inflammatory disease of the conjunctiva and cornea, i.e. conjunctivitis or keratoconjunctivitis
- The primary disease occurs in kittens and is accompanied by signs of systemic infection such as fever, lethargy, upper respiratory disease, and inflammatory disease widespread on mucosal epithelial surfaces, as well as ocular disease
  - Biopsies are seldom submitted from cats with primary disease, but FHV-1 infection likely plays an important role in feline symblepharon formation (see above) and neonatal corneal defects (see Ch. 8)
- The virus becomes dormant in the trigeminal ganglion and stress-related recrudescence leads to clinical disease involving the conjunctiva and cornea. Prior or recrudescent FHV-1 infection may contribute to chronic stromal keratitis, corneal stromal sequestration or eosinophilic keratitis that may be biopsied in adult cats (see Ch. 8)
- There are no morphologic hallmarks that allow the pathologist to establish a cause-and-effect relationship in FHV-1 conjunctivitis, so the importance of the role of FHV-1 in non-specific feline conjunctivitis is not well understood
- Distinct morphologic patterns of conjunctivitis that might be related to FHV-1 recrudescence include eosinophilic conjunctivitis and keratoconjunctivitis.

Eosinophilic keratoconjunctivitis (see also Ch. 8) (Fig. 7.40)

- Blepharitis involving the eyelid margins, conjunctivitis and keratitis associated with eosinophilic inflammation are common clinical presentations in cats. Lesions may occur together or separately, and may be uni- or bilateral
- Morphologic features include:
  - Eosinophilic keratoconjunctivitis is a regional lesion which often extends onto the corneal surface but does not involve the deep stroma
  - There is irregular distortion of the surface contour of the cornea, with or without ulceration
  - There is often a plexus of relatively large blood vessels within the underlying stroma

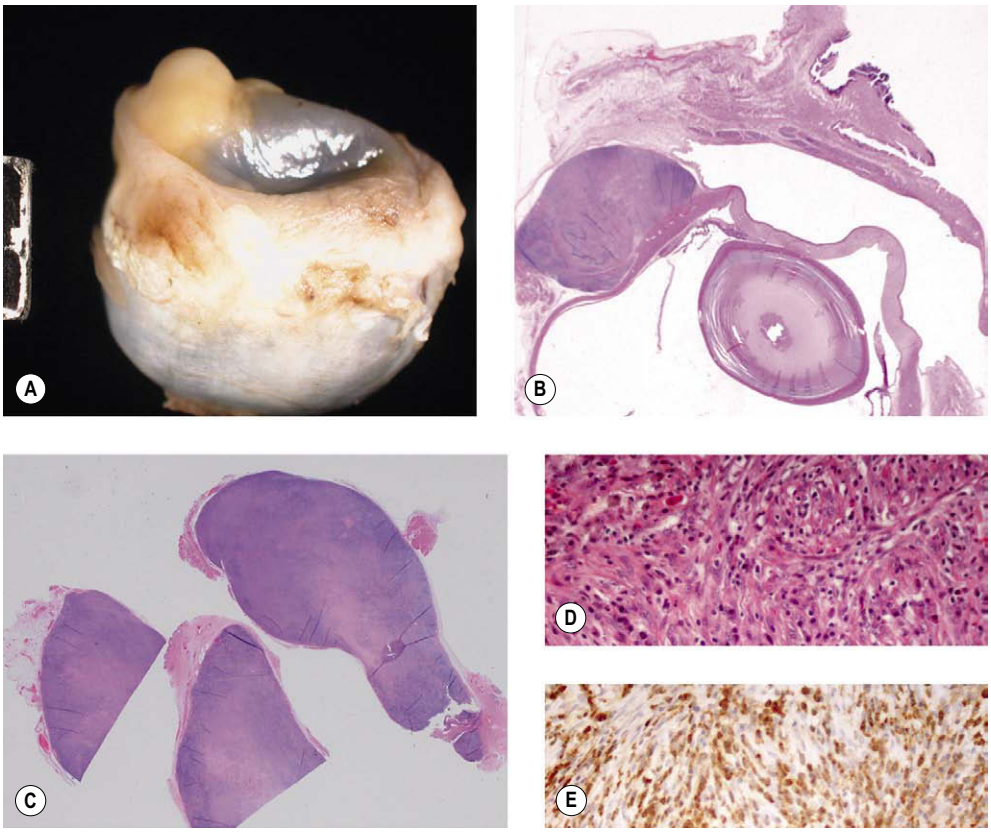


Figure 7.37 Nodular granulomatous episcleritis (NGE), pathology. (A,B) Gross photograph and low magnification photomicrograph showing features of a particularly large and invasive nodular granulomatous episcleritis. The infiltrate is sharply delineated, composed of granulomatous and lymphocytic inflammatory infiltrate, and the epithelium is intact. (C) Low magnification photomicrograph of a typical biopsy specimen of NGE showing the sharply delimited margins typical of the disease. (D,E) Photomicrographs of a spindle cell lesion (D) showing positive immunolabeling for the macrophage marker CD18 (E).

  - Lympho-plasmacytic inflammatory cells may out-number eosinophils
- The role played by FHV-1 infection in the development of feline eosinophilic ocular disease remains controversial, despite the findings of studies that provide molecular evidence of prior or active FHV-1 infection.

Feline conjunctival papillary mastocytosis (Fig. 7.41)

This is an uncommon disease. There are seven cases in the COPLOW collection.

- This presents as a poorly delineated, proliferative conjunctival lesion and most of the samples submitted are from the palpebral surface of the nictitans
- The underlying cause remains unknown
- Morphologic features of feline conjunctival papillary mastocytosis include:
  - Papillary proliferation of an intact epithelium
  - Mixed inflammatory infiltrate and edema in the substantia propria
  - Large numbers of mast cells including many mast cells directly within or on the surface of the conjunctival epithelium.

Lipogranulomatous conjunctivitis in cats (Fig. 7.42)

- Feline lipogranulomatous conjunctivitis presents as a regional, nodular disease which usually involves the palpebral conjunctiva from the lid margin to the fornix. Less frequently, the bulbar conjunctiva or the nictitans are involved
- Reports suggest that older cats with sparse peri-ocular pigmentation (e.g. orange cats) are predisposed. There are 81 cases in the COPLOW collection diagnosed as feline lipogranulomatous conjunctivitis:
  - 28 of the 81 cases have a concurrent neoplasm including 17 cases with conjunctival squamous cell carcinoma
  - Pathologists should be aware that lipogranulomas and neoplasia may go together. Thus, a careful search should be made to rule out neoplasia
- The lesions, involving the palpebral conjunctiva, are non-ulcerative, nodular, and pale in color, ranging from opaque white to light yellow
- Characteristic morphologic features include:
  - A bland granulomatous inflammatory reaction surrounding large, cell-free lakes of lipid dissolved during processing
  - Large empty spaces which may be surrounded by inconspicuous multi-nucleated macrophages
  - In some areas, and in some lesions, the characteristic profile is that of solid sheets of large, multinucleate, foreign body macrophage cells, or of smaller epithelioid cells with foamy cytoplasm
  - Lympho-plasmacytic or suppurative inflammation are seldom prominent.

Plasmacytic conjunctivitis ('plasmoma') of the nictitans in dogs

- This is a common clinical presentation in breeds that are predisposed to chronic superficial keratitis (CSK), in

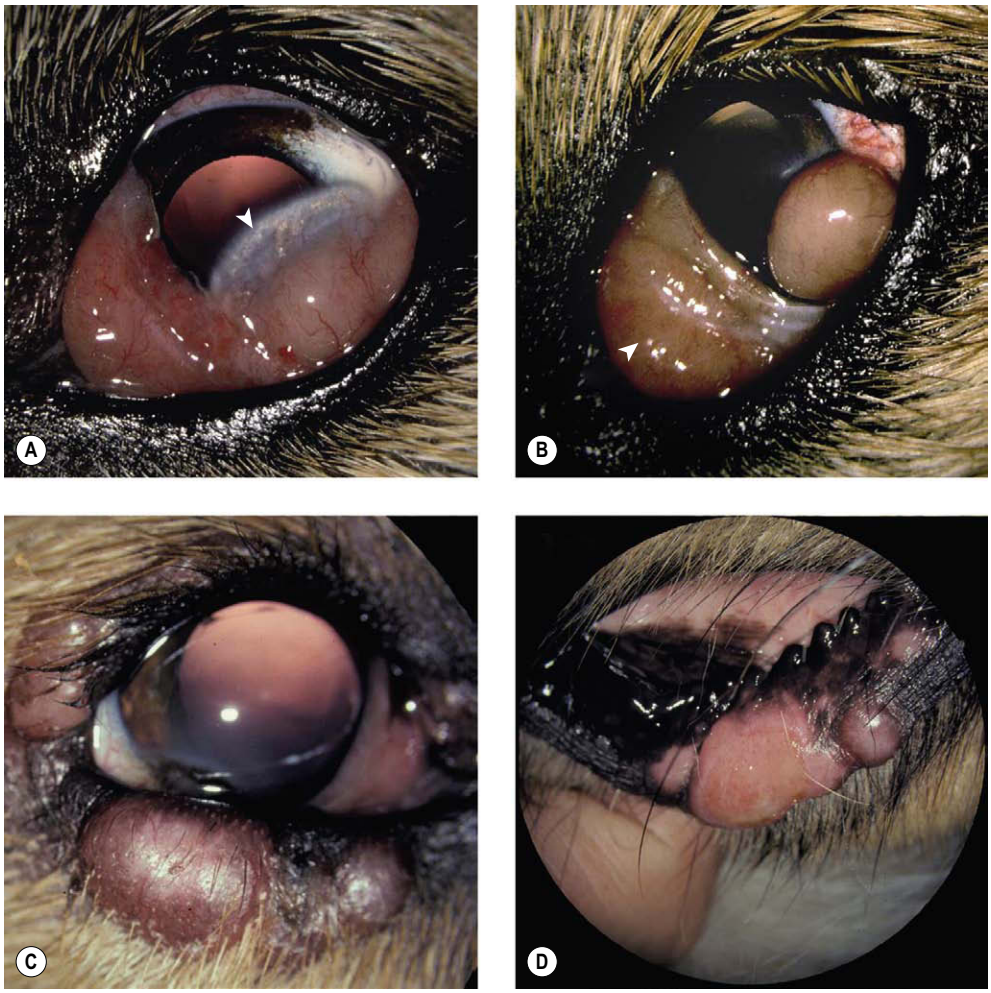


Figure 7.38 Proliferative keratoconjunctivitis in Collie dogs. (A) Collie, 3 years old: the nictitans and inferior limbus are involved. Corneal lipid keratopathy (arrow) is present at the leading edge of this pseudotumor. (B) Collie, 2 years old: a solitary temporal mass and an elevated lesion of the nictitans can be seen at the arrow. (C) Collie, 2 years old: the most remarkable lesions were the lid involvement in both eyes. A small limbal mass was present inferior. (D) This is the lower lip of the dog in (C). All lesions biopsied were indicative of this disease.

which conjunctivitis may accompany keratitis, or occur in isolation
- Thickening and hyperemia of the nictitating membrane, with depigmentation of the leading edge, is observed bilaterally
- The disease is considered to have a similar immunopathogenesis to CSK, which is discussed in further detail in Chapter 8.

Triamcinolone (depot corticosteroid preparation) injection site granulomas (Fig. 7.43)

- Several inflammatory conditions of the eye or conjunctiva are treated by sub-conjunctival injection of a long-acting corticosteroid preparation
- The injected formulation is associated with a distinctive granulomatous inflammatory reaction, with the following characteristics:
  - Reaction to recently injected product is characterized by the presence of an acellular, flocculent, amphophilic material with scant macrophage cells
  - The mature granuloma is characterized by a cell-free center, surrounded by epithelioid or multinucleate macrophage cells
  - Macrophage cells have a, very distinctive, rounded rectangular, clear vacuole in the cytoplasm
  - The granuloma may be surrounded by minimal lymphoplasmacytic infiltrate or minimal fibrosis.

Canine conjunctival onchocerciasis (Fig. 7.44)

- This parasitic condition is discussed in detail elsewhere in this text (Ch. 6)
- In North America, the disease has been recorded in the Western United States, in or near California
- The conjunctival manifestations of this disease may be recognized as a raised, irregular inflammatory lesion of the limbal conjunctiva that may be submitted as a biopsy specimen
- Morphologic features that should point toward the diagnosis of onchocerciasis include:
  - Tissue fibrosis
  - An eosinophilic component to the inflammatory response
  - A granulomatous component to the inflammatory response.

Equine onchocerciasis

- Microfilaria of *Onchocerca cervicalis* have been proposed as a cause of inflammation and depigmentation of the temporal limbal conjunctiva in horse

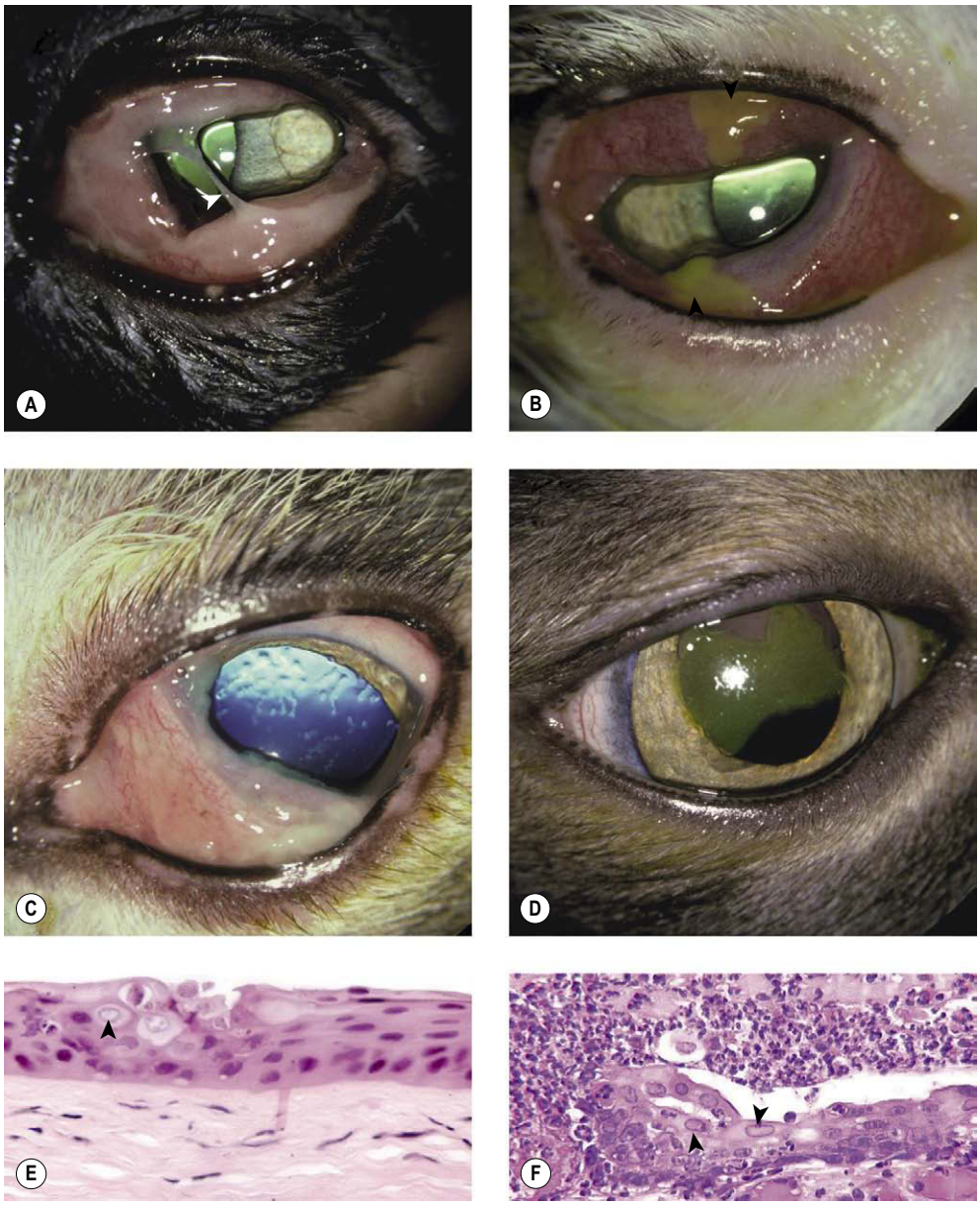


Figure 7.39 Feline herpetic keratoconjunctivitis. (A) DSH, 8 months old: moderate chemosis and hyperemia are present. An adhesion is forming (arrow) between the superior and inferior palpebral conjunctiva. (B) DSH, 1 year old: moderate chemosis and hyperemia are present. Two areas of epithelial erosion have retained fluorescein stain (arrows). (C) DSH, 1 year old: the nictitans is hyperemic and prolapsed. Multiple punctate corneal opacities indicative of FHV-1 can be seen by retroillumination. (D) DSH, 8 years old: a large superficial corneal ulcer has been stained with fluorescein dye. (E,F) Photomicrographs showing epithelial cell necrosis and intranuclear inclusion bodies (arrows) in feline herpes conjunctivitis.

- However, the causal relationship between onchocerciasis and ocular lesions in horses has not been definitively established.

CONJUNCTIVAL NEOPLASMS AND OTHER NODULAR LESIONS

Conjunctival squamous cell carcinoma

Equine squamous cell carcinoma (Figs 7.45, 7.46)

There are 80 cases of conjunctival squamous cell carcinoma in the COPLOW collection, 10% of equine submissions.

- This is a relatively common condition in horses, and demonstrates increasing incidence with age
- Ultraviolet (UV) light exposure is thought to be involved in the pathogenesis of equine conjunctival squamous cell carcinoma for the following reasons:
  - A high percentage of these neoplasms have mutant p53 protein/altered p53 expression
  - Ocular squamous cell carcinoma has a higher prevalence in those geographic regions where UV light exposure is likely to be greater
  - Squamous cell carcinoma is more likely to occur in horses that are lacking in conjunctival and peri-ocular melanin pigment
  - Solar elastosis and actinic keratosis is often seen in association with the early stages of disease
    - Deep in the connective tissue the normal collagen matrix is disrupted by areas with an amphophilic matrix deposition, often with wavy elastin fibers

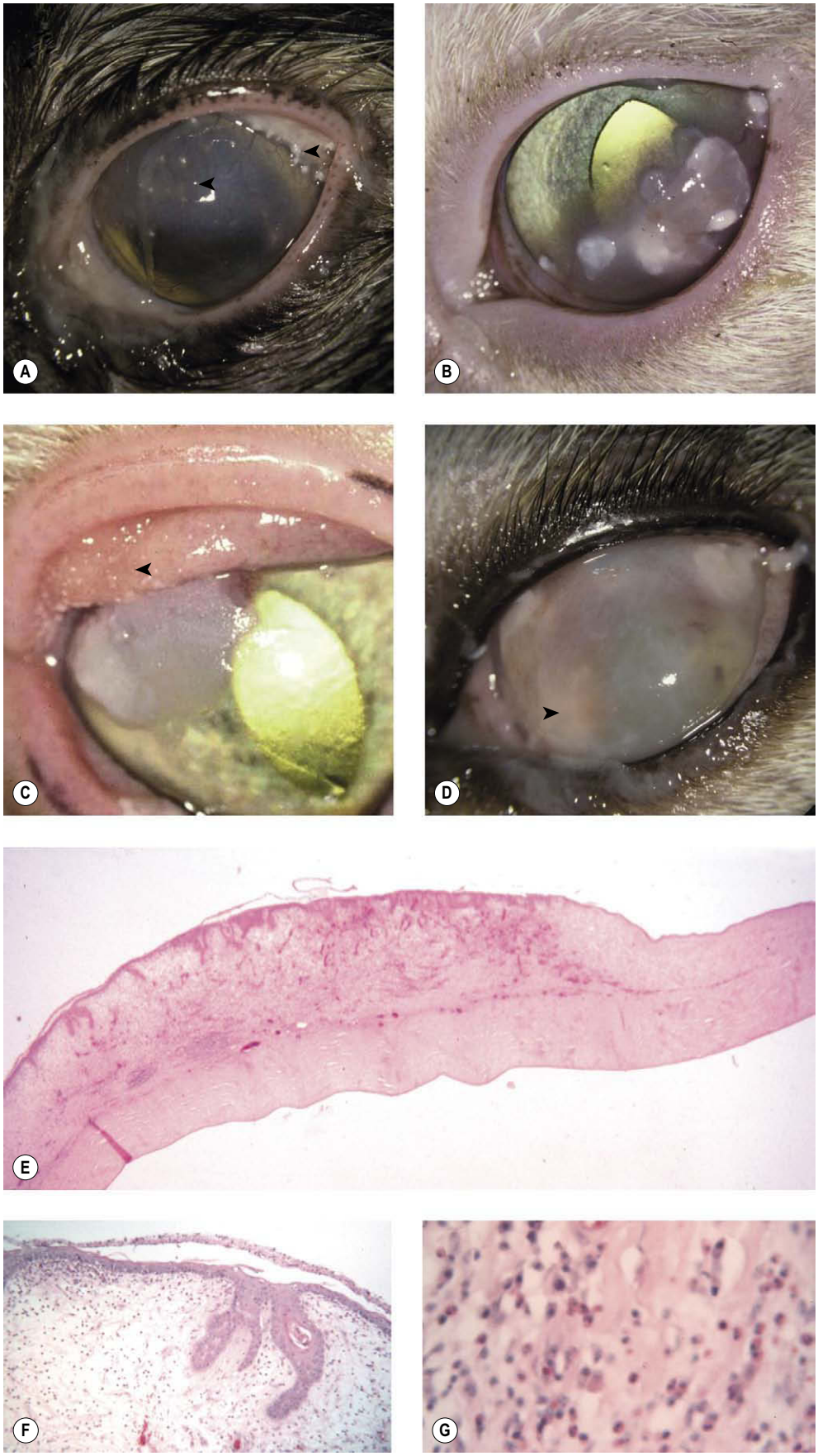


Figure 7.40 Feline eosinophilic keratoconjunctivitis. (A) DSH, 3 years old: lid margin depigmentation, diffuse corneal vascularization, and focal white superficial corneal and conjunctival precipitates (arrows) are present. (B) DSH, 4 years old: multiple elevated white plaques are superficial to the corneal vascularization. (C) DSH, 9 years old: a large white gritty deposit is present temporally. Fine precipitates are present over the severely hyperemic conjunctiva (black arrow). Dendritic ulcers were also present. (D) DSH, 4 years old: severe corneal edema and vascularization are present. White precipitates can be seen in the superficial epithelium (arrow). (E) Low magnification photomicrograph of a keratectomy specimen showing distinct regional superficial disease. The affected tissue is raised, edematous and highly vascularized. (F) Higher magnification photomicrograph showing the intact epithelium with marked epithelial downgrowth and edematous stroma. (G) High magnification photomicrograph showing a few eosinophils.

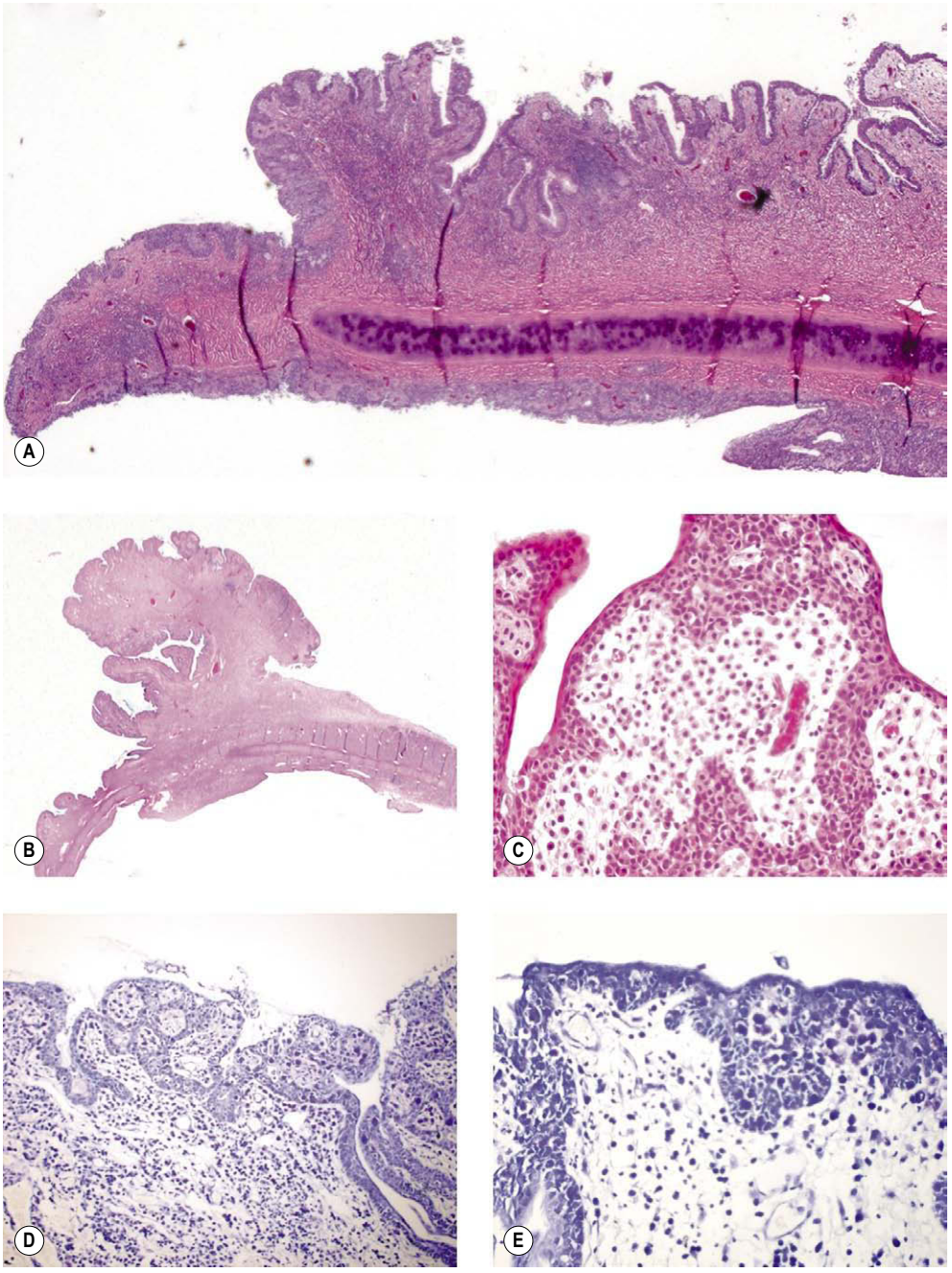


Figure 7.41 Feline conjunctival papillary mastocytosis. (A,B) Low magnification photomicrographs showing a papillary anterior surface proliferation on the palpebral surface of the third eyelid typical of feline conjunctival papillary mastocytosis. (C) Photomicrograph showing a complex interdigitating intact epithelium and edematous stroma. (D,E) Photomicrographs of affected conjunctiva showing mast cells largely within the epithelium (toluidine blue stain).

  - Stains for elastin are positive, or stain a 'murky' gray rather than the distinct black staining of individual elastin fibers
- Biopsy is done at all stages of this disease process, and multiple stages may be represented within the conjunctival tissues of an individual subject, so one will see a variety of morphological presentations:
  - Dysplastic epithelium, presumed to be pre-neoplastic:
    - Disorganization of epithelium, or abnormal keratinization patterns
    - Minimal anaplastic cellular features
    - Does not invade the epithelial basal lamina
  - Carcinoma *in situ*
    - Epithelial disorganization and atypical keratinization deep within the epithelium (dyskeratosis)
    - Anaplastic cellular features
      - Large nucleus to cytoplasm ratio
      - Karyomegaly
      - Binucleate cells
      - Large nucleoli
    - Affected cells do not extend beyond the epithelial basal lamina
  - Non-invasive squamous cell carcinoma
    - Fully neoplastic epithelial features with invasion beyond the basal lamina
    - Atypical features of keratin formation such as keratin pearls
    - Infiltration of lymphatic or vascular structures is not seen

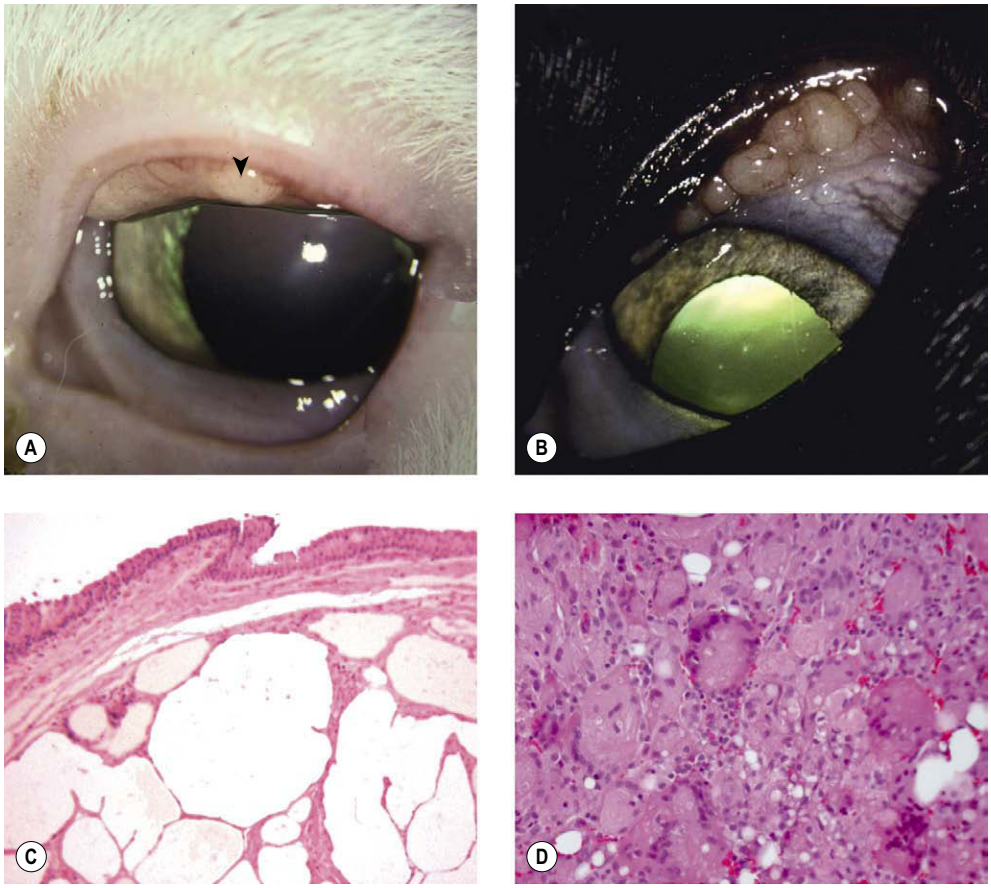


Figure 7.42 Feline lipogranulomatous conjunctivitis. (A) DSH, 9 years old: this white opaque deposit (arrow) was present in the superior subpalpebral area in both eyes. (B) DSH, 8 years old: in this bilateral case, the subconjunctival lesions were more lobulated. (C) Photomicrograph showing large empty spaces, 'lipid lakes', surrounded by macrophage cells. (D) Photomicrograph showing huge multinucleated giant cells and lipid.

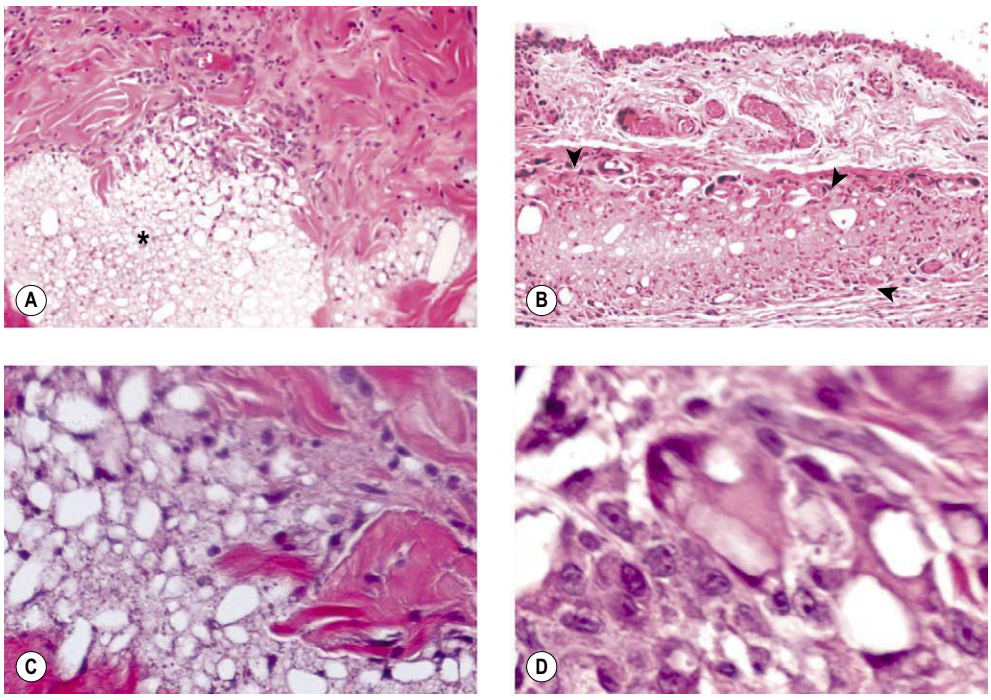


Figure 7.43 Corticosteroid suspension (Depo-Medrol) injection granuloma. (A) Photomicrograph showing a developing granuloma at the site of a subconjunctival corticosteroid suspension product injection. Centrally, there is a large amount of vacuolated foreign (*) material and only a few phagocytes at the margins. (B) Photomicrograph showing a more mature granuloma at a subconjunctival injection site. A distinct granuloma (arrows) is seen in the substantia propria of the conjunctiva. (C,D) Higher magnification showing macrophage cells with distinctive, nearly rectangular empty spaces typical of an injection granuloma with a suspension product.

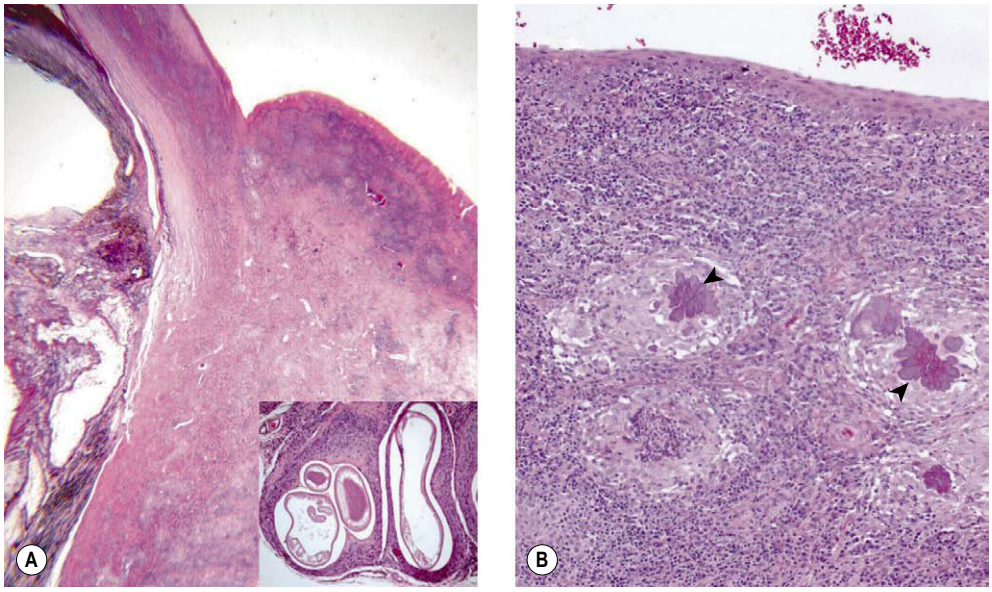


Figure 7.44 *Onchocerca* conjunctivitis. (A) Low magnification photomicrograph of the limbus with swollen inflamed reaction. The inset shows adult male and female *Onchocerca* nematodes in a granulomatous space deep within the conjunctiva. (B) Photomicrograph showing Splendore-Hoeppli reaction (arrows) away from obvious nematodes.

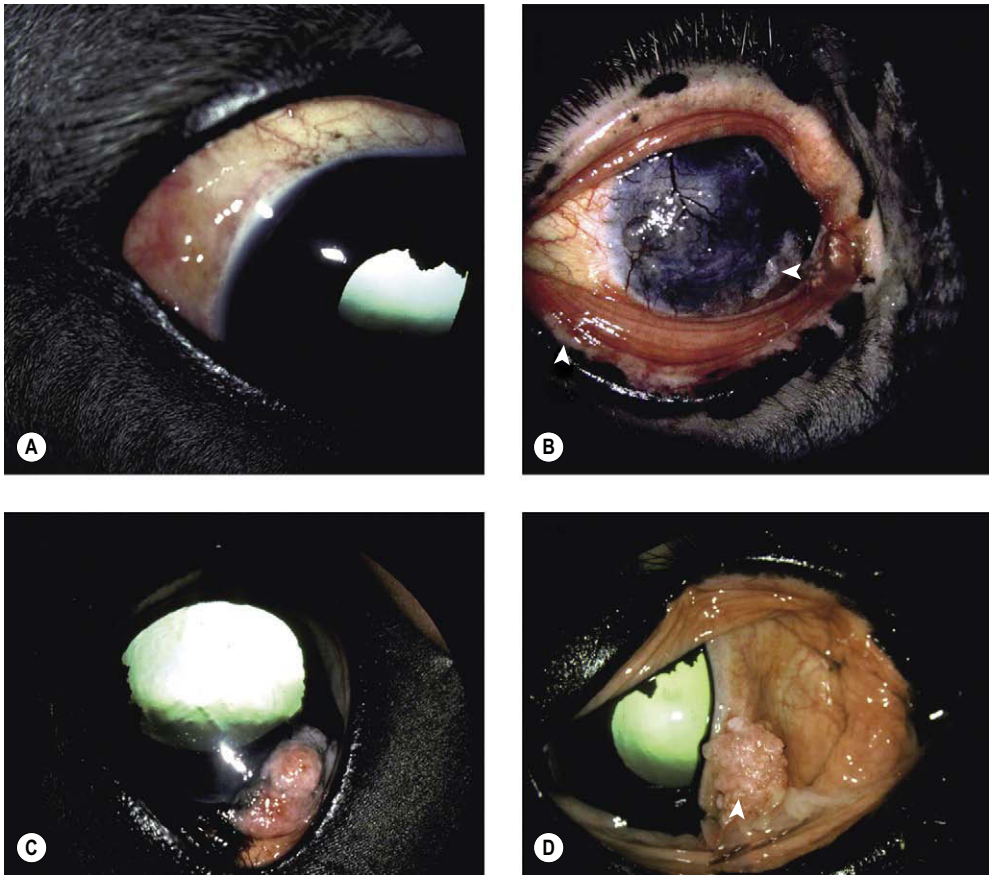


Figure 7.45 Equine conjunctival squamous cell carcinoma, clinical. (A) Thoroughbred, 7 years old: the hyperemic elevated mass has not invaded the cornea. (B) Grade horse, 20 years old: squamous cell carcinoma was confirmed at the limbus and lid margin (arrows). (C) American Saddlebred Horse, 5 years old: this temporal proliferative mass invaded the cornea. (D) Thoroughbred, 20 years old: the cerebriform elevated SCC was restricted to the palpebral surface of the nictitans (arrow).

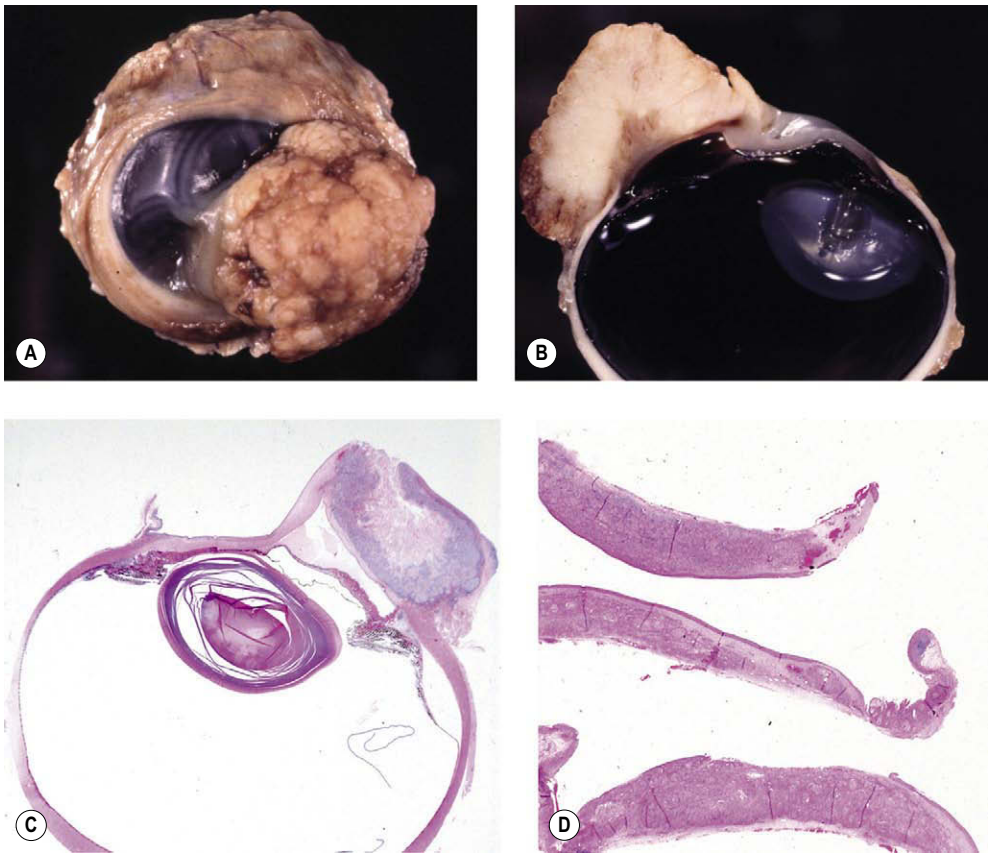


Figure 7.46 Equine squamous cell carcinoma, pathology. (A,B) Gross photographs of a horse with exophytic, poorly invasive, limbal squamous cell carcinoma. (C) Subgross photomicrograph showing an exophytic, and also invasive, squamous cell carcinoma. (D) Subgross photomicrograph showing invasion into the corneal stroma.

  - Desmoplastic, stromal fibrous proliferation is not seen or is not prominent
- Invasive squamous cell carcinoma
  - Deep invasion of the sub-epithelial tissues is a prominent feature with vascular invasion or lymphatic invasion
  - Individual neoplastic cells are often seen and they may be difficult to distinguish from stromal spindle cells
- Stromal invasive squamous cell carcinoma (Fig. 7.47)
  - This distinctive variant invades the cornea specifically and will be discussed further in Chapter 8.

Bovine squamous cell carcinoma (Fig. 7.48)

Bovine ocular squamous cell carcinoma is very common but underrepresented in the COPLOW collection. This may result from a bias towards companion animals in clinical veterinary ophthalmology, the client base for a mail-in comparative ocular pathology service. There are 16 submissions of ocular squamous cell carcinoma in cattle, representing 18.8% of all bovine submissions.

- Squamous cell carcinoma is the second most frequently reported tumor of cattle with only lymphoma being more common
- Most common in the Hereford breed and its crosses, that show a characteristic lack of periocular pigment
- The condition is often bilateral
- More common when the conjunctiva is not pigmented
- An estimated 75% occur on the bulbar conjunctiva at the limbus and the rest are widely dispersed
- UV light is thought to be an important factor in pathogenesis
- The morphologic subtypes are similar to those of the horse, except there is no reported equivalent of the stromal invasive form.

Canine squamous cell carcinoma (Fig. 7.49)

Conjunctival squamous cell carcinoma is very uncommon in dogs. There are 24 cases in the COPLOW collection, representing 0.4% of all canine tumor submissions.

- The morphologic variations are similar to those seen in other species.

Feline squamous cell carcinoma (Fig. 7.50)

Conjunctival squamous cell carcinoma is relatively rare in cats. There are 61 cases in the COPLOW collection, representing 2.2% of feline tumor submissions.

- A higher proportion of the feline tumors are highly invasive, extending into the globe
- Care must be taken to rule out metastatic squamous cell carcinoma because tumors of the lung or middle ear can spread to the conjunctival area
- Multicentric squamous cell carcinoma is mentioned above. This tumor is associated with epithelial dysplasia or neoplastic transformation of the conjunctival epithelium or corneal epithelium and should be ruled out in all cases.



Figure 7.47 Equine stromal invasive squamous cell carcinoma. (A) Clinical photograph showing a horse with an opaque cornea as a result of a stromal invasive squamous cell carcinoma. (B) Gross photograph of an equine eye with stromal invasive squamous cell carcinoma. There is a smooth surface because the invasion is inward to the corneal stroma and not outward. (C,D) Low magnification photomicrographs showing invasion of the lamellar stroma by neoplastic epithelial cells in stromal invasive squamous cell carcinoma.

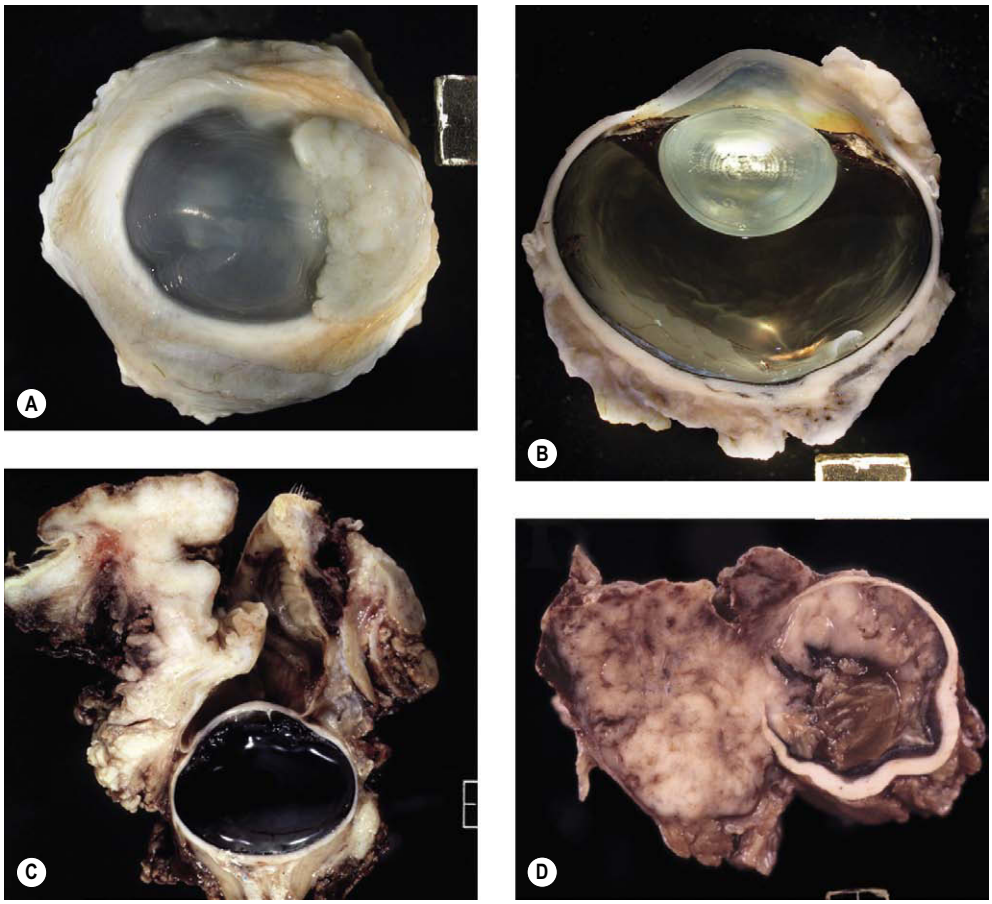


Figure 7.48 Bovine ocular squamous cell carcinoma. (A,B) Gross photographs of a bovine eye with a limbal exophytic squamous cell carcinoma. (C) Gross photograph of a bovine eye with a less circumscribed conjunctival tumor. (D) A bovine globe largely effaced by an aggressive invasive squamous cell carcinoma.

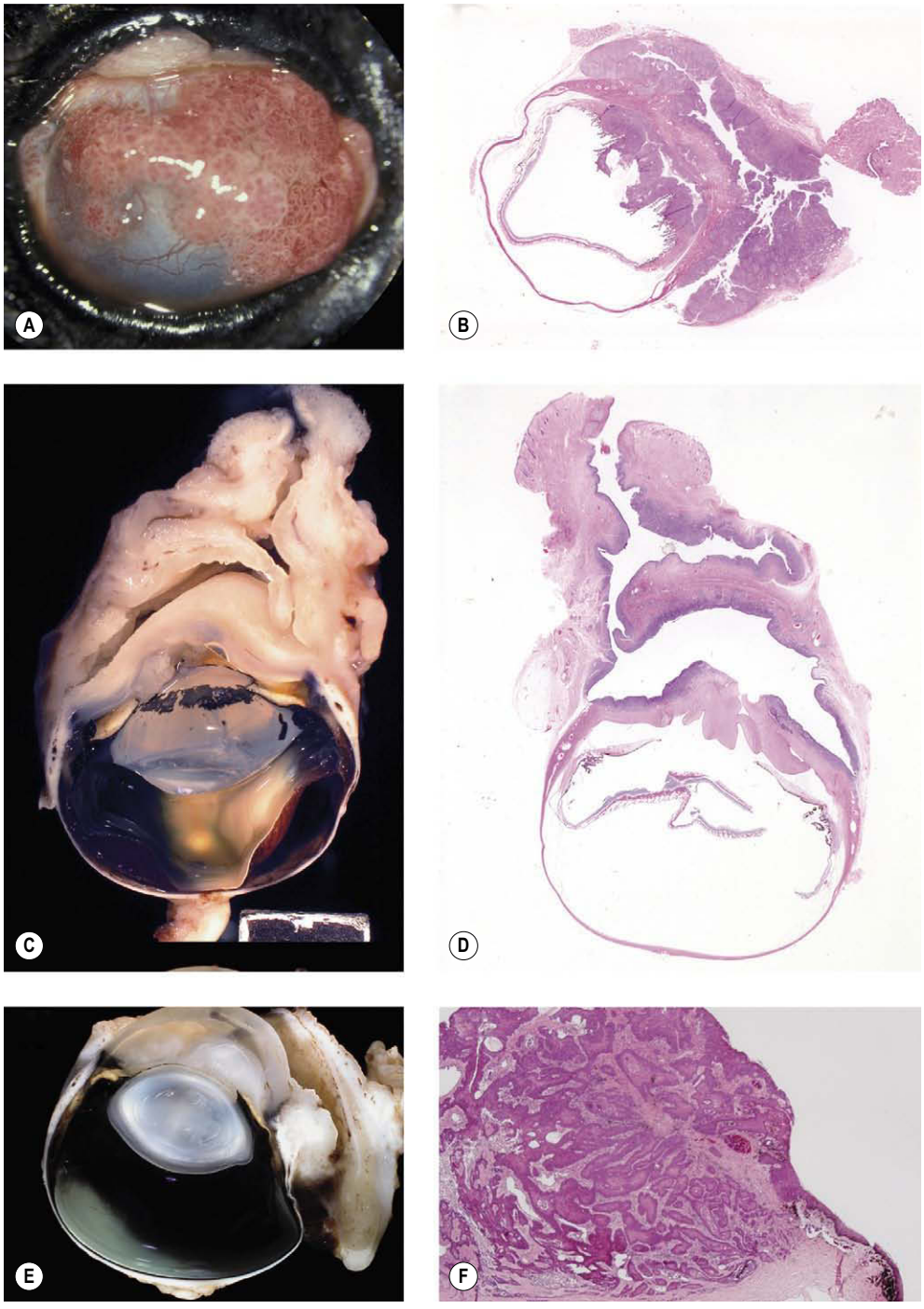


Figure 7.49 Canine conjunctival/corneal squamous cell carcinoma. (A) Toy Poodle, 9 years old: this rapidly proliferating limbal squamous cell carcinoma originated in the superior and temporal palpebral conjunctiva and extended over the cornea. (B) Subgross photograph showing extensive invasive squamous cell carcinoma involving the conjunctiva and extending into the globe. (C,D) Gross and subgross photographs showing canine conjunctival squamous cell carcinoma with extensive conjunctival spread in a dog with concurrent chronic inflammation. (E,F) Gross photograph and photomicrograph of a dog with more localized squamous cell carcinoma at the limbus.

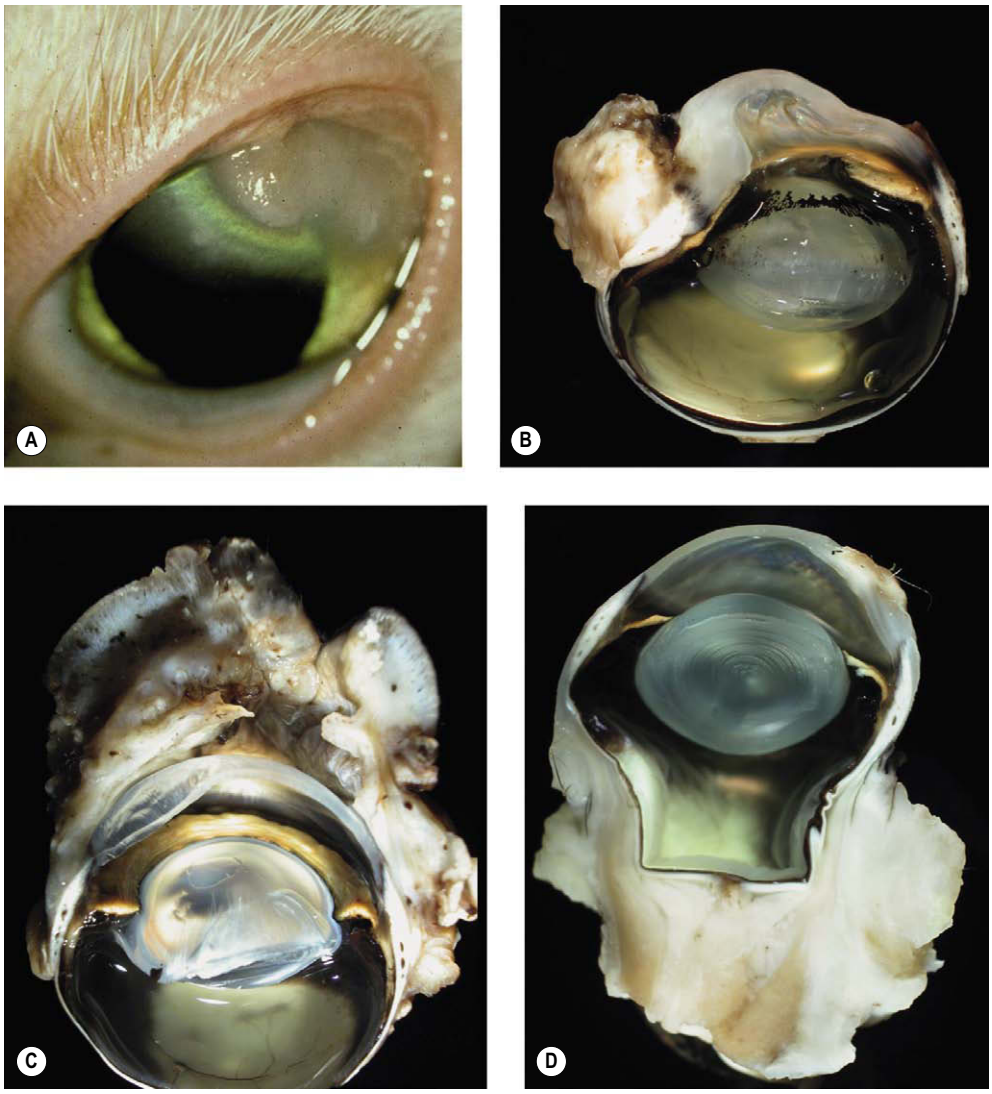


Figure 7.50 Feline conjunctival/corneal squamous cell carcinoma. (A) DSH, 6 years old: the proliferative mass originated in the temporal conjunctiva. (B–D) Gross photographs of feline conjunctival squamous cell carcinoma showing various degrees of invasion.

Comparative Comments

- Considering precancerous lesions and cancerous lesions of the surface epithelium, there appears to be a close association between the entities seen in humans and in other species
- In humans, the term 'conjunctival intraepithelial neoplasia' (CIN) is used to describe a spectrum of patterns of cellular proliferation, extending from dysplasia to carcinoma *in situ*. Tumors with this designation have not penetrated the underlying basement membrane
- Frank squamous cell carcinoma of the conjunctiva is an uncommon tumor in humans, occurring most frequently in tropical countries.

Feline conjunctival mucoepidermoid carcinoma (Fig. 7.51)

Although this tumor is not reported in the literature, there are 10 cases in the COPLOW collection.

- Morphologic features of conjunctival mucoepidermoid carcinoma:
  - The primary cell is a poorly-differentiated secretory cell forming acinar or tubular features
  - The tumors often form papillary fronds on the conjunctival surface but they also invade into the tissue
  - Too little is known about this neoplasm to speculate as to the prognosis.

Canine conjunctival melanoma and melanocytoma (Figs 7.52, 7.53)

There are 149 cases of canine conjunctival melanocytic tumors in the COPLOW collection, representing 2.6% of canine tumor submissions.

- Of the canine conjunctival melanocytic tumors in the COPLOW collection, 81% are malignant by morphologic criteria and 19% are melanocytoma
- By histologic observation, most of the affected dogs have pigmentation of their normal conjunctival tissues
- The breeds most commonly affected by conjunctival melanocytic tumors are retrievers, Rottweilers, and Cocker spaniels

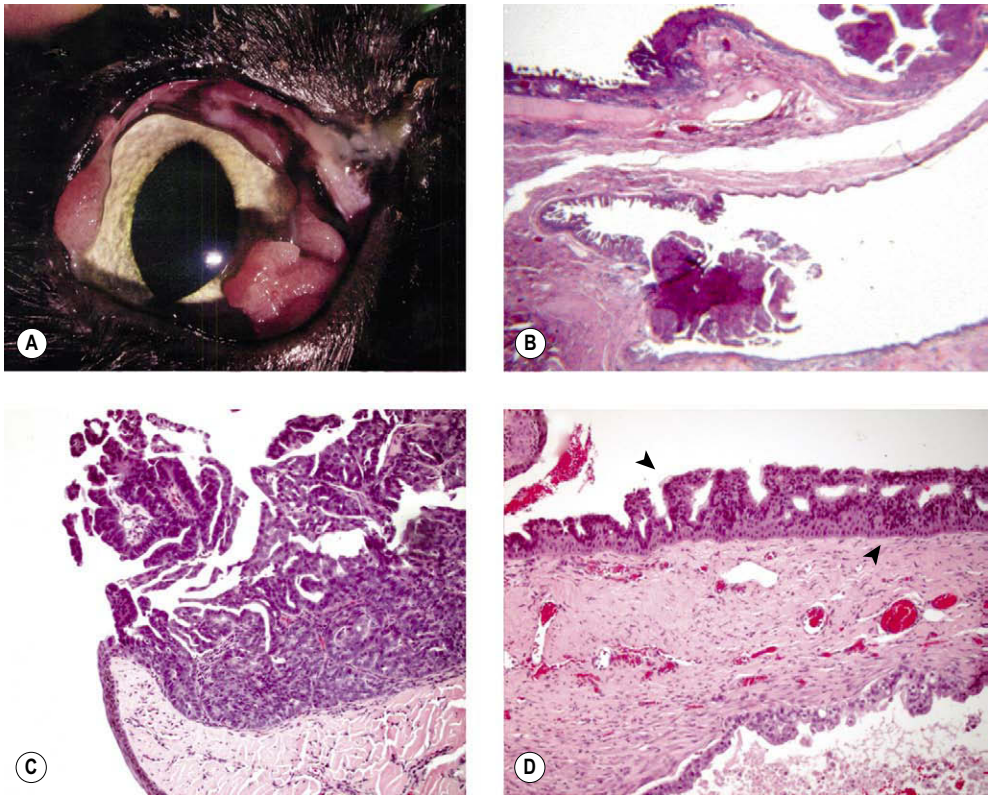


Figure 7.51 Feline conjunctival mucoepidermoid carcinoma. (A) Clinical photograph showing papillary and multifocal lesions. (B,C) Low magnification photomicrographs showing surface oriented mucoepidermoid carcinoma, characterized by a papillary growth pattern and local invasion. (D) Photomicrograph showing neoplastic cells spread over the surface replacing the native epithelium (arrows).

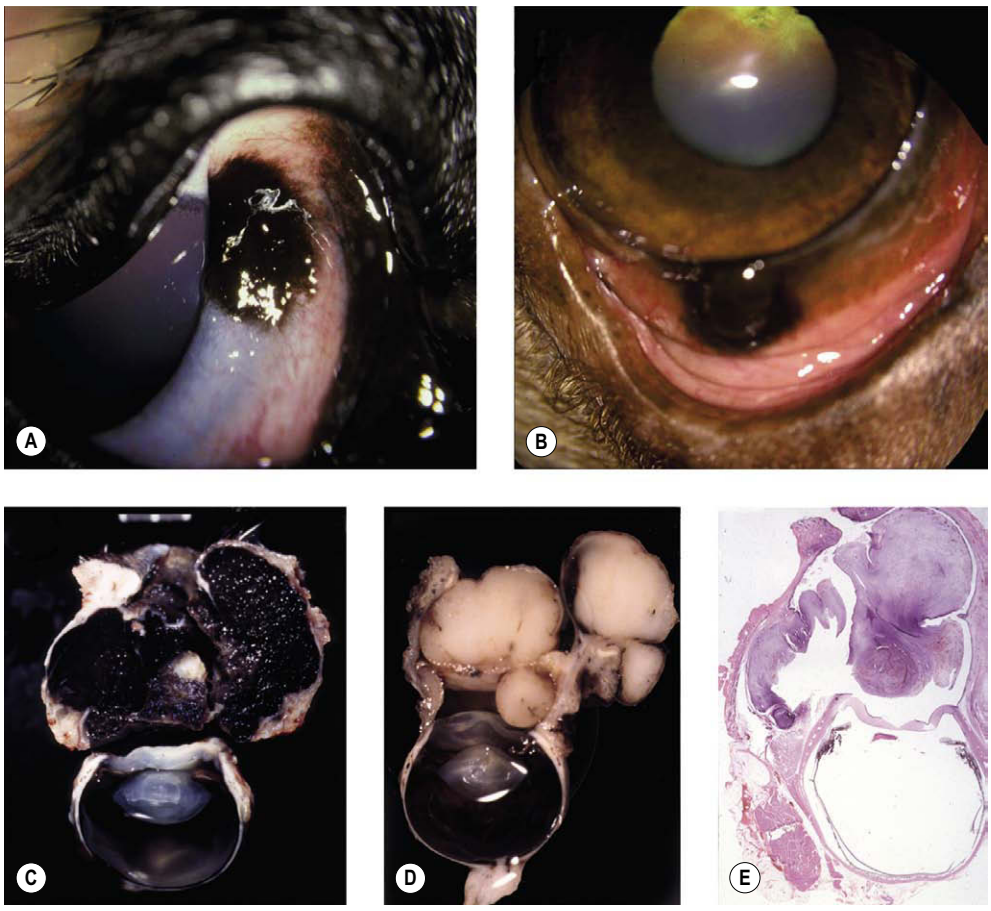


Figure 7.52 Canine conjunctival melanocytoma/melanoma. (A) Bluetick Coonhound, 8 years old: this pigmented lesion on the nictitans was a melanocytoma. (B) Chesapeake Bay Retriever, 11 years old: involving the palpebral surface and free margin of the nictitans, this was a melanoma on biopsy. (C,D) Gross photographs showing widespread recurrence of canine conjunctival melanoma. (E) Subgross photomicrograph of widespread recurrence of canine conjunctival melanoma.

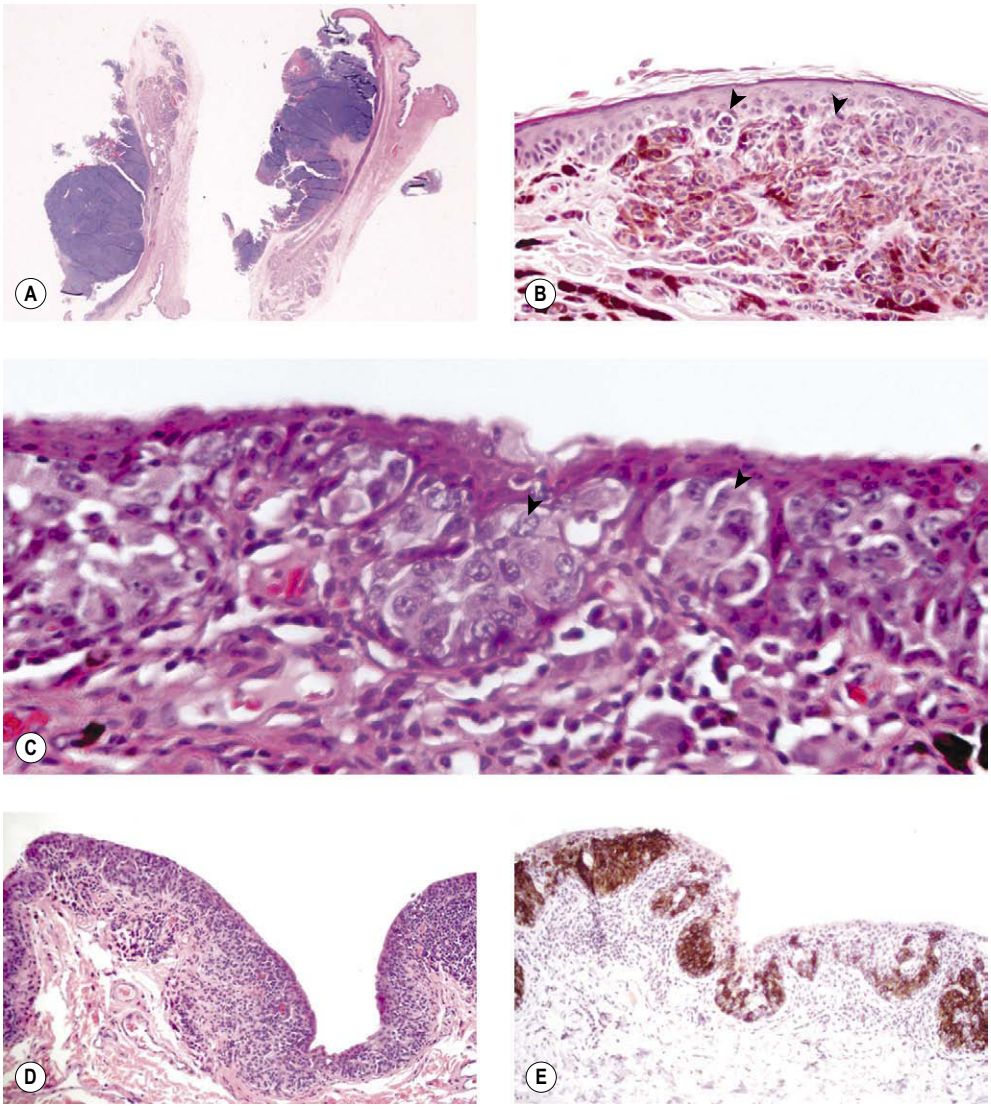


Figure 7.53 Canine conjunctival melanoma, microscopic. (A) Subgross photomicrograph showing the bulbar surface of the excised third eyelid with conjunctival melanoma. (B,C) Pigmented and non-pigmented melanoma cells abutting and within the epithelium (arrows). (D,E) Photomicrographs of conjunctival tissue well away from the tumor mass showing aggregates of tumor cells (D). Melan-A immunohistochemistry highlights the neoplastic cells within the conjunctival epithelium (E).

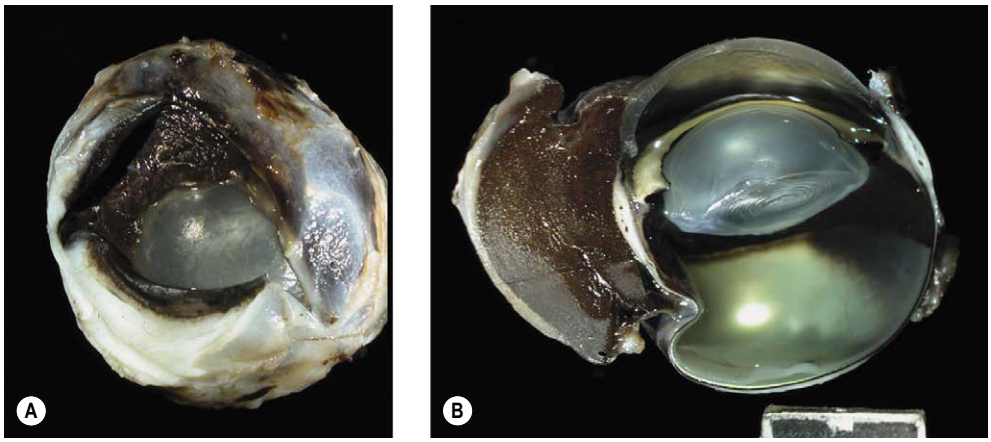


Figure 7.54 Feline conjunctival melanoma. (A,B) Gross photographs showing the typical appearance of feline conjunctival melanoma. Pigmented tumor is nestled deeply in the episcleral connective tissue.

- It is noteworthy that, despite their intraocular pigmentary problems that lead to glaucoma, there are no Cairn Terriers with conjunctival melanomas
- Morphologic features of canine conjunctival melanocytoma
  - Melanocytomas were always heavily pigmented
  - The cells are mostly large heavily pigmented round cells, mixed with pigmented spindle cells
  - Melanocytoma, like melanoma cells, tend to form tight aggregates or clusters subtending or within the conjunctival epithelium
  - No satellite aggregates of neoplastic or dysplastic melanocytic cells were apparent within the conjunctival epithelium away from the tumor location
- Morphologic features of canine conjunctival melanoma
  - Melanomas have variable pigmentation but many in the COPLOW collection were totally amelanotic
  - The tumor cells had anaplastic features:
    - Large single nucleoli are a common and useful diagnostic feature that point to the melanocytic origin of tumors
    - Large nucleus to cytoplasm ratio
    - Hyper-chromatic nuclear profiles
    - Abundant mitotic activity
  - Neoplastic cells near the conjunctival epithelium tend to form aggregated clusters, and are often seen within the epithelium
    - This feature is useful in recognizing tumors as being of melanocytic origin but it is not a feature which predicts biological behavior
  - Many of the melanomas had dysplastic or neoplastic melanocytic cells subtending or within the epithelium well away from the site of the primary mass
- Of 23 cases where the location of the primary mass was known, 61% were on the third eyelid, 22% were on the bulbar conjunctiva, and 17% were on the palpebral conjunctiva
- Follow-up information was available for only 21 cases
  - Half of the tumors recurred in the conjunctiva, often away from the primary site or multi-focally
  - Metastasis was only documented in two of these 21 cases and both of these were neoplasms that originally involved the palpebral conjunctiva
- Recommendations based on known behavior:
  - Careful observation for local recurrence followed by aggressive surgical excision (with enucleation of the globe) after the first recurrence.

Feline conjunctival melanoma (Fig. 7.54)

There are 26 conjunctival melanocytic tumors in cats, representing 0.9% of feline tumor submissions.

- All 26 cases had a malignant potential
  - There was a wide variation in the degree of pigmentation
  - Some of these malignant neoplasms have shown aggressive infiltration or metastatic disease, despite features that would suggest benign behavior in dogs
    - This feature is similar to the reported behavior of cutaneous melanoma in cats
  - The most common location for the primary tumor is the bulbar conjunctiva with extension deep into the orbit adjacent to the globe.

Comparative Comments

- Melanocytic neoplasia in humans is seen more frequently in the pathology laboratory than other precancerous lesions and cancerous lesions of the surface epithelium
- These melanocytic lesions may occur as congenital or acquired, benign or malignant lesions. Nevocellular nevi are the most common conjunctival tumors. The malignant potential of these nevi vary, with junctional and compound nevi thought to have low malignant potential, while the subepithelial nevus usually remains benign
- Primary acquired melanosis (PAM) is a condition seen in adults as stippled brown conjunctival pigmentation. The onset is usually at 40–50 years of age and includes a spectrum that extends from benign acquired melanosis (PAM without atypia) to PAM with mild, moderate, or severe atypia. PAM with atypia can evolve into melanoma
- Approximately 50% of conjunctival melanomas arise de novo, and 50% arise from acquired melanosis or conjunctival nevi
- The histopathologic features of conjunctival melanoma in humans have prognostic significance for survival. Metastases are more likely to occur in invasive melanomas that are more than 0.8 mm thick.

Canine conjunctival hemangioma, hemangiosarcoma (Fig. 7.55)

There are 230 canine conjunctival tumors of vascular endothelial origin in the COPLOW collection, representing 4% of canine tumor submissions.

- Of these, 65% are diagnosed as hemangioma and 35% are diagnosed as hemangiosarcoma
- The features that distinguish between hemangioma and hemangiosarcoma are:
  - The degree of differentiation of blood-filled vascular spaces
  - The presence of anaplastic features in the neoplastic cells
  - The extent to which the tumor is infiltrative
- Tumors most commonly occur on the leading edge of the nictitans, or on the temporal bulbar conjunctiva
- The clinical presentation of bright red, exophytic, friable, bleeding mass lesions is similar for both hemangioma and hemangiosarcoma
- Previous authors have speculated that UV light exposure is a risk factor in the pathogenesis of conjunctival vascular endothelial tumors in dogs. The COPLOW collection supports this hypothesis for the following reasons:
  - Almost all of the conjunctival tissue sampled away from the mass lesion is non-pigmented
  - There is a trend for affected dogs to be from regions with a higher ambient UV light exposure
  - The most frequent tumor locations are consistent with the conjunctival locations subject to the highest light exposure, i.e. the leading, exposed portion of the nictitans and the temporal bulbar conjunctiva
  - Dogs from the hound and sporting breeds are over-represented in the affected group. These dogs are more likely to be kept outdoors, with greater exposure to sunlight than typical domestic pet dogs.

Feline conjunctival hemangioma, hemangiosarcoma (Fig. 7.56)

There are a total of 16 vascular endothelial tumors of the conjunctiva in cats in the COPLOW collection, representing 0.5% of feline tumor submissions. There are 11 hemangiomas and five hemangiosarcomas.

- The numbers are too low to allow conclusions to be drawn regarding their biologic behavior
- Morphologically, the tumors have similar features to the canine vascular endothelial tumors described above.

Equine hemangioma, hemangiosarcoma, angiosarcoma

There are six cases in the COPLOW collection, representing 3.6% of equine tumor submissions.

- This tumor has also been reported as angiosarcoma in the veterinary literature, due to reluctance on the part of those authors to designate the origins of the neoplasm as vascular or lymphatic endothelial cells. However, all six cases in the COPLOW collection were designated as hemangioma or hemangiosarcoma
- There are reports of this tumor arising within the cornea and, consistent with this observation, one of the five COPLOW appeared to arise within the corneal stroma
- Widely disparate biological behaviors have been attributed to this tumor type. Limited follow-up information was available, but one of the COPLOW cases recurred after local excision.

Canine conjunctival mast cell tumor (Fig. 7.57)

There are 32 cases of canine conjunctival mast cell tumors in the COPLOW collection, representing 0.5% of canine tumor submissions.

- Although the same grading criteria might be used as for cutaneous mast cell tumors, there are no follow-up studies that establish the prognostic value of this grading scheme in conjunctival mast cell tumor
- In the collection there are tumors on the palpebral conjunctiva, the bulbar conjunctiva and the nictitans but most of the submissions do not specify mass location.

Feline conjunctival mast cell tumor

There are only four cases of feline conjunctival mast cell tumor in the COPLOW collection.

Canine conjunctival lymphoma (Fig. 7.58)

There are 19 cases of canine conjunctival lymphoma in the COPLOW collection, representing 0.3% of canine tumor submissions.

- Six are simply designated lymphoma and four are epitheliotropic lymphoma, mycosis fungoides.

Feline conjunctival lymphoma

There are 10 cases of feline conjunctival lymphoma in the COPLOW collection, representing 0.4% of feline tumor submissions.

- None of these are considered epitheliotropic.

Comparative Comments

As described in other species, tumors of lymphocytic or hemopoietic origin are seen in humans, as well as tumors of adnexal origin together with Kaposi's sarcoma (described above).

Tumors of the canine third eyelid gland (nictitans gland) (Fig. 7.59)

- There are 109 cases of epithelial tumors of the nictitans gland in the COPLOW collections, representing 1.9% of canine tumor submissions. Within this series, there is a spectrum of different morphological types of tumors:
  - Adenoma (13 cases)
  - Complex and mixed tumors
  - Adenocarcinoma (53 cases)
- Local invasion with recurrent growth is common but metastasis is rare.

Tumors of the feline third eyelid gland (nictitans gland) (Fig. 7.60)

There are 19 tumors of the third eyelid in cats in the COPLOW collection, representing 0.7% of feline neoplasms.

- All of these are recorded as adenocarcinoma.

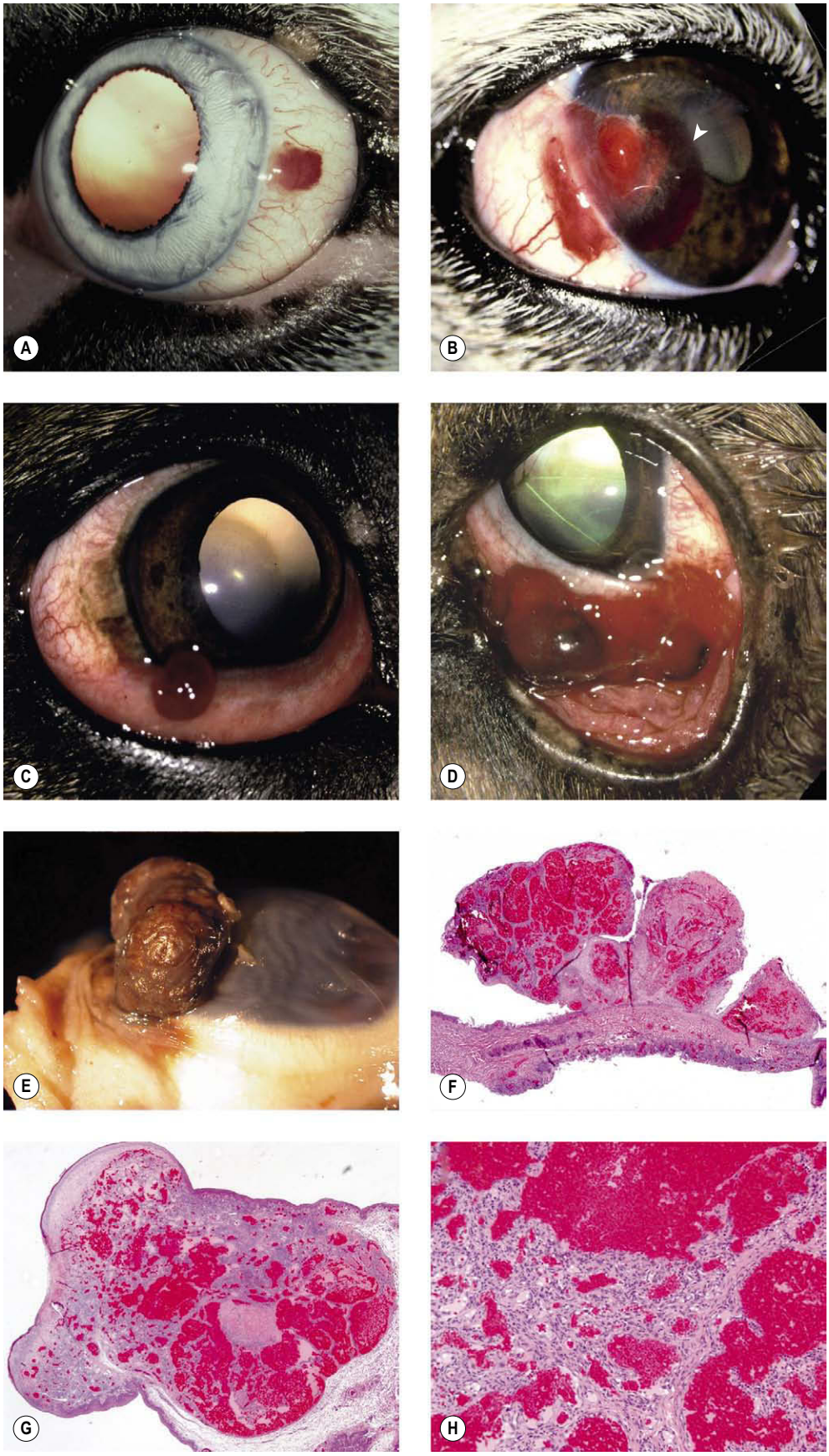
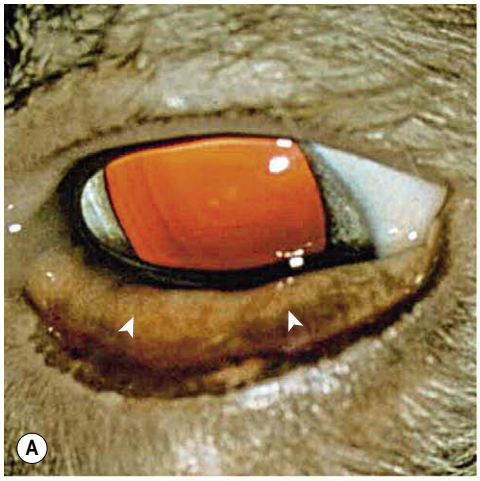


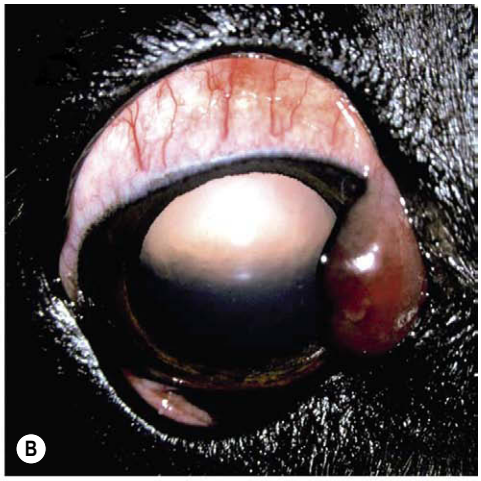
Figure 7.55 Canine conjunctival hemangioma/hemangiosarcoma. (A) Boxer, 8 years old: histopathology confirmed this focal conjunctival lesion was a hemangioma. (B) Beagle, 11 years old: this hemangioma involved the temporal conjunctiva and cornea. Intrastromal hemorrhage is also present (arrow). (C) German Shepherd Dog cross, 12 years old: limited to the margin of the nictitans, this mass was diagnosed as a hemangiosarcoma. (D) Basset Hound, 9 years old: this extensive hemangioma involved the palpebral surface of the nictitans and bulbar surface of the globe. (E) Gross photograph of limbal hemangiosarcoma. (F,G) Low magnification photomicrographs showing exophytic tumors, characterized by vascular channels of various diameter, that form a distinct nodular mass lesion. (H) Higher magnification showing dilated vascular pattern and also less-differentiated endothelial cells in disorganized sheets.

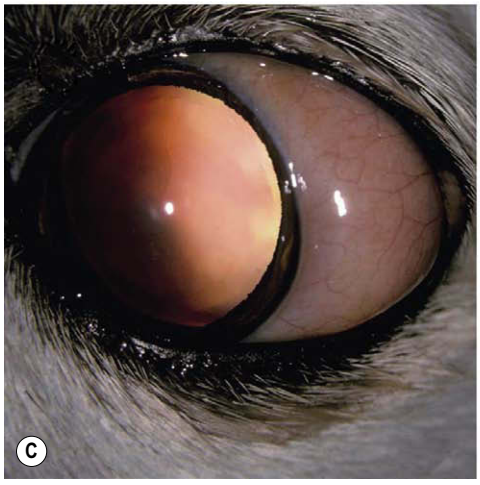




Figure 7.56 Feline conjunctival hemangioma/hemangiosarcoma. (A,B) Gross photograph and subgross photomicrograph of a cat globe showing a solid tan mass (hemangiosarcoma) adherent to the sclera at the equator extending to the limbus. (Reproduced with permission from Pirie C G, Dubielzig R R 2006 Feline conjunctival hemangioma and hemangiosarcoma: a retrospective evaluation of eight cases (1993–2004). Vet. Ophthalmol. 9:227–231.)







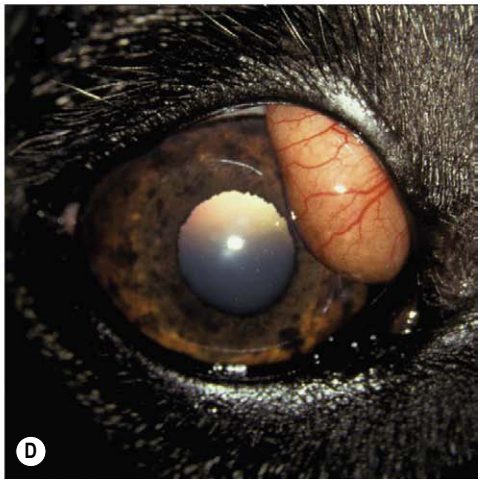


Figure 7.57 Conjunctival mast cell tumor, clinical. (A) Siamese, 8 years old: the entire length of the inferior palpebral conjunctiva was involved (arrows). (B) Labrador Retriever, 7.5 years old: this reddish-gray mass originated from the medial bulbar conjunctiva. (C) American Eskimo Dog, 6 years old: diffuse swelling with chemosis and hyperemia of the temporal bulbar conjunctiva. (D) Mixed Breed, 9 years old: pale yellowish mass originated in the superior bulbar conjunctiva.

Canine viral papilloma (Fig. 7.61)

In the COPLOW collection, there are 24 cases of canine viral papilloma occurring on the conjunctiva of dogs, representing 0.16% of canine submissions.

- Viral papilloma is a wart-like, exophytic, cutaneous growth associated with a papilloma virus
- The classical location for canine disease is in the oral cavity, however mucous membranes anywhere are susceptible, as is haired skin
- This is characteristically a lesion seen in young dogs, immune-suppressed adult dogs, or at the site of trauma or surgery
- Viral papilloma is self-limiting, however, it may be irritating and disfiguring

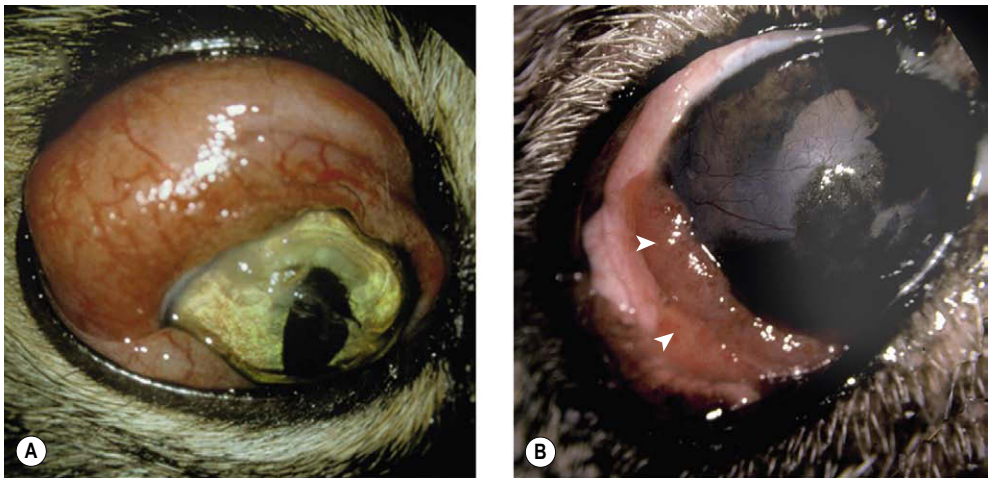


Figure 7.58 Conjunctival lymphoma, clinical. (A) Persian, 5 years old: the large firm mass in the superior bulbar conjunctiva resulted in lagophthalmos. (B) English Bulldog, 9 years old: this hyperemic conjunctival mass (arrows) started inferior temporal limbus. The pigmentary keratitis is the result of keratoconjunctivitis sicca.

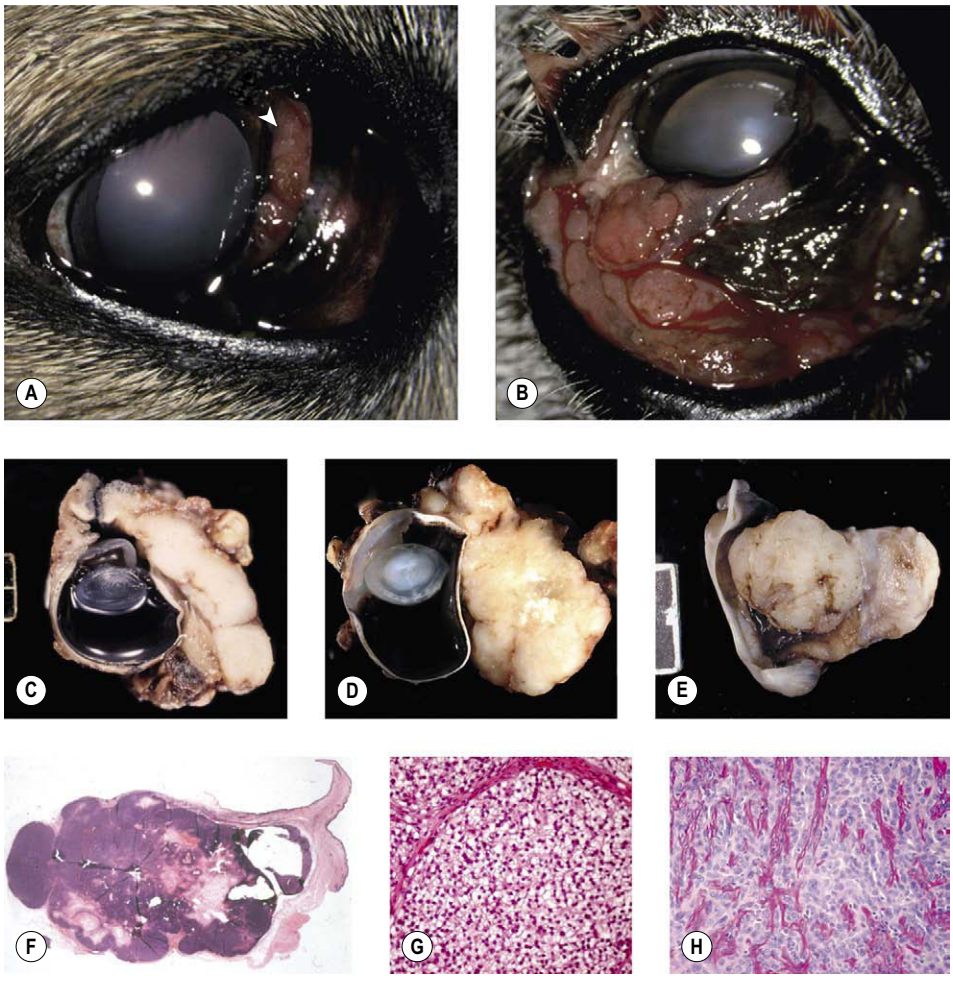


Figure 7.59 Canine adenocarcinoma of the gland of the third eyelid. (A) Mixed Breed, 12 years old: the thickened prolapsed nictitans has a tumor mass (arrow) extending from its bulbar surface. Histopathology confirmed an adenocarcinoma of the nictitans gland. (B) Mixed Breed, 15 years old: an adenocarcinoma was diagnosed from a biopsy specimen of this thickened and hemorrhagic nictitans. (C,D) Gross photographs showing the third eyelid gland tumor as a lobulated tan mass pushed deeply into the soft tissues of the ventral medial orbit, while the globe is unaffected. (E) Gross photograph of the dissected third eyelid with a smaller mass bulging on the bulbar aspect of the gland. (F) Subgross photomicrograph of the sectioned third eyelid showing a lobulated mass effacing the gland. (G) Photomicrograph showing a solid but bland tumor with vacuolated neoplastic epithelial cells. (H) Photomicrograph showing adenocarcinoma with PAS-positive mucin (PAS stain).

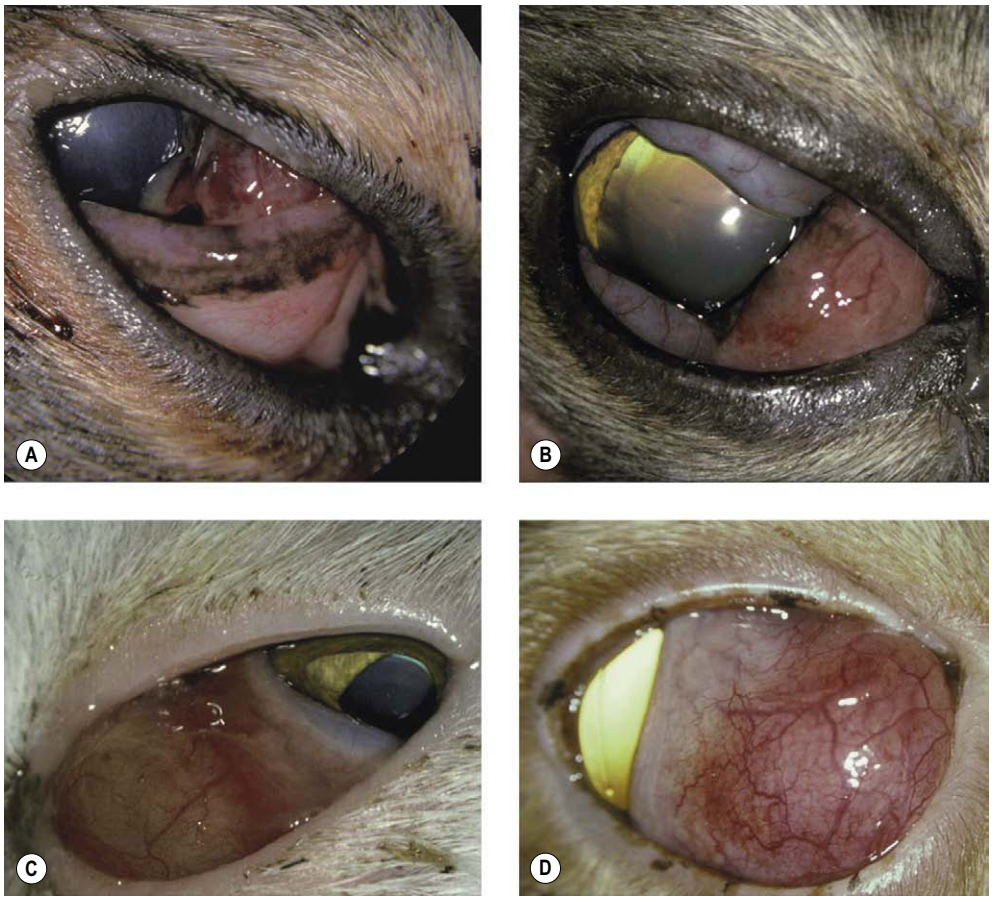


Figure 7.60 Feline third eyelid gland tumors, clinical. (A) DSH, 9 years old: the mass protruding from the bulbar surface of the otherwise normal looking nictitans was diagnosed as a nictitans adenocarcinoma. (B) DSH, 18 years old: the free lid margin is difficult to view in this diffusely swollen nictitans. A squamous cell carcinoma arising within the nictitans gland was diagnosed by biopsy. (C) DSH, 11 years old: this pale yellowish mass extended to the base of the nictitans but did not involve the leading edge. A fibrosarcoma was diagnosed by histopathology. (D) DSH, 5 years old: evaluation of a fine needle aspirate confirmed lymphoma as the cause of this smooth hyperemic swelling.

- Characteristic morphologic features include:
  - An exophytic, papillary mass made up almost entirely by hyperplastic epithelium and long, thin cores of vascular stroma
  - Hyperkeratosis which might be parakeratotic or orthokeratotic
  - Prominent widening of the stratum granulosum with large keratohyalin granules
  - The presence of koilocytes within the stratum granulosum, which represent a hallmark feature
    - Koilocytes are rounded cells in, or near, the stratum granulosum. They have clear amphophilic cytoplasm and may or may not contain keratohyalin granules
  - Rare intranuclear basophilic viral inclusion bodies are seen.

Cysts of the conjunctiva

- Congenital cysts of the lacrimal canaliculi or other ectopic ductular structures
  - These occur as watery-fluid filled cysts under the conjunctival or medial canthal epithelium in young animals
  - Histologically, there is little or no inflammation and the cysts often have a distinctive double epithelium
- Acquired ductular cysts
  - These are usually derived from lacrimal ducts and are secondary to obstruction and/or inflammation
- Inclusion cysts (Fig. 7.62)
  - These are usually secondary to trauma and entrapment of conjunctival surface epithelium
  - They appear as opaque, white, round sub-epithelial nodules
  - They can occur anywhere and often contain keratin
- Proliferative inflammatory lesions can often masquerade as neoplasia.

Conjunctival squamous papilloma and reactive papilloma (Fig. 7.63)

- There are 81 squamous papillomas of the conjunctiva in the COPLOW collection, representing 0.54% of all canine submissions.
  - Squamous papilloma is a discrete arborizing papillary lesion usually on the conjunctival surface. There is no underlying tumor or inflammation and the arborizing units end with a sharp angle.
- There are 167 reactive papillomas in the COPLOW collection representing 1.1% of canine submissions.
  - Reactive papillomas are very localized, exophytic, arborizing, papillary growths characterized by a basal stalk and rounded, blunt papillary 'arms'
  - They usually occur at the lid margin and are often seen superficial to inflammation or a meibomian gland tumor
- There are no dysplastic or anaplastic epithelial features
- The cause is unknown
- The prognosis is excellent.

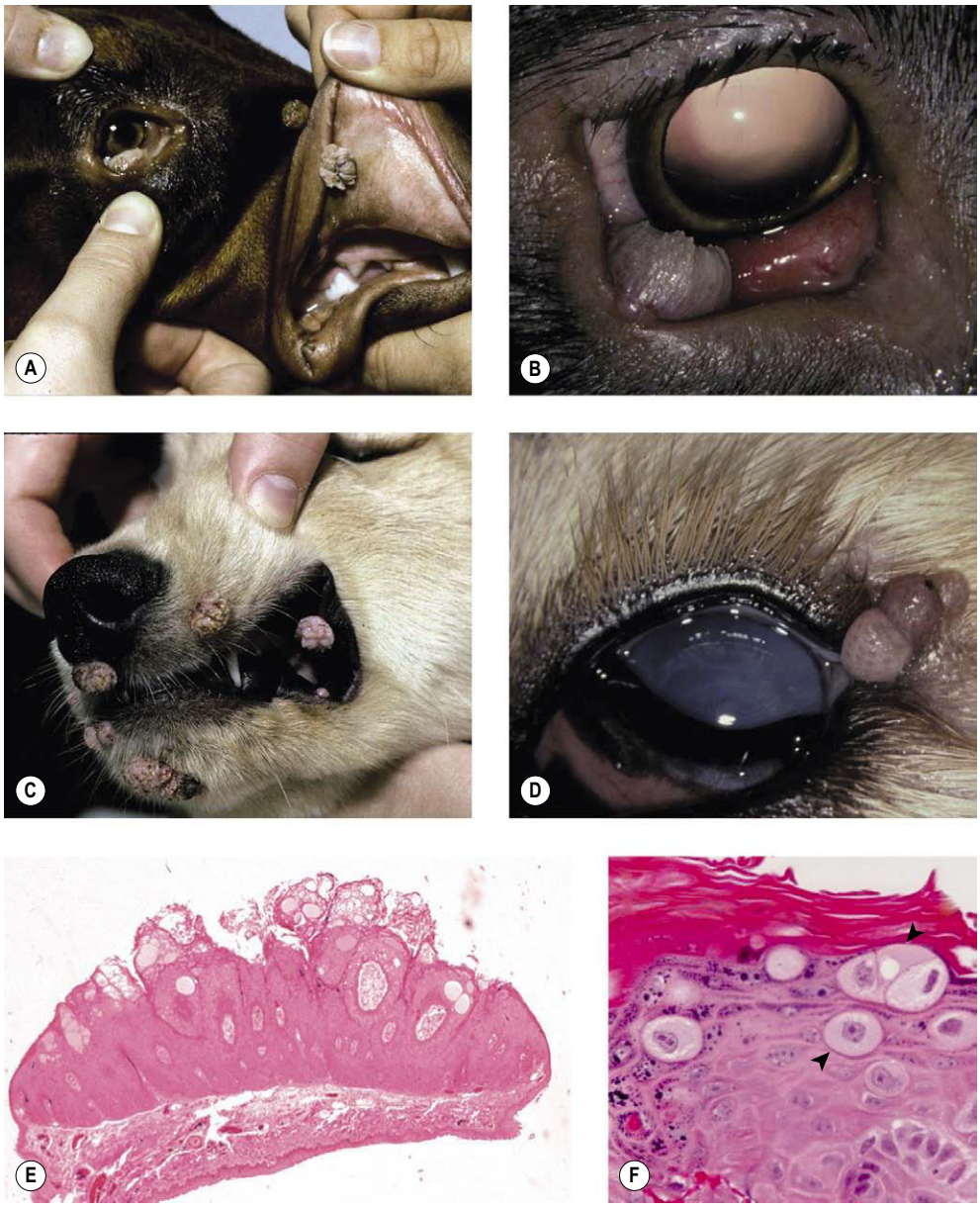


Figure 7.61 Canine viral papilloma. (A) Doberman Pinscher, 5.5 months old: A papillomas can be seen on the lower lid and on the buccal mucosa. (B) Doberman Pinscher, 5.5 months old: this littermate of the dog shown in (A) demonstrates a typical papilloma. The third eyelid appears as a hyperemic mass to the right of the papilloma due to eversion of the cartilage of the nictitans. (C) Golden Retriever, 15 weeks old: multiple rostral and buccal papillomas are present. (D) Periocular papillomas are present in the dog in (C). The globe was phthisical as a result of trauma at birth. (E) Low magnification photomicrograph showing an exophytic papillary tumor typical of viral papilloma. (F) Photomicrograph showing koilocytes (arrows) in the stratum granulosum.

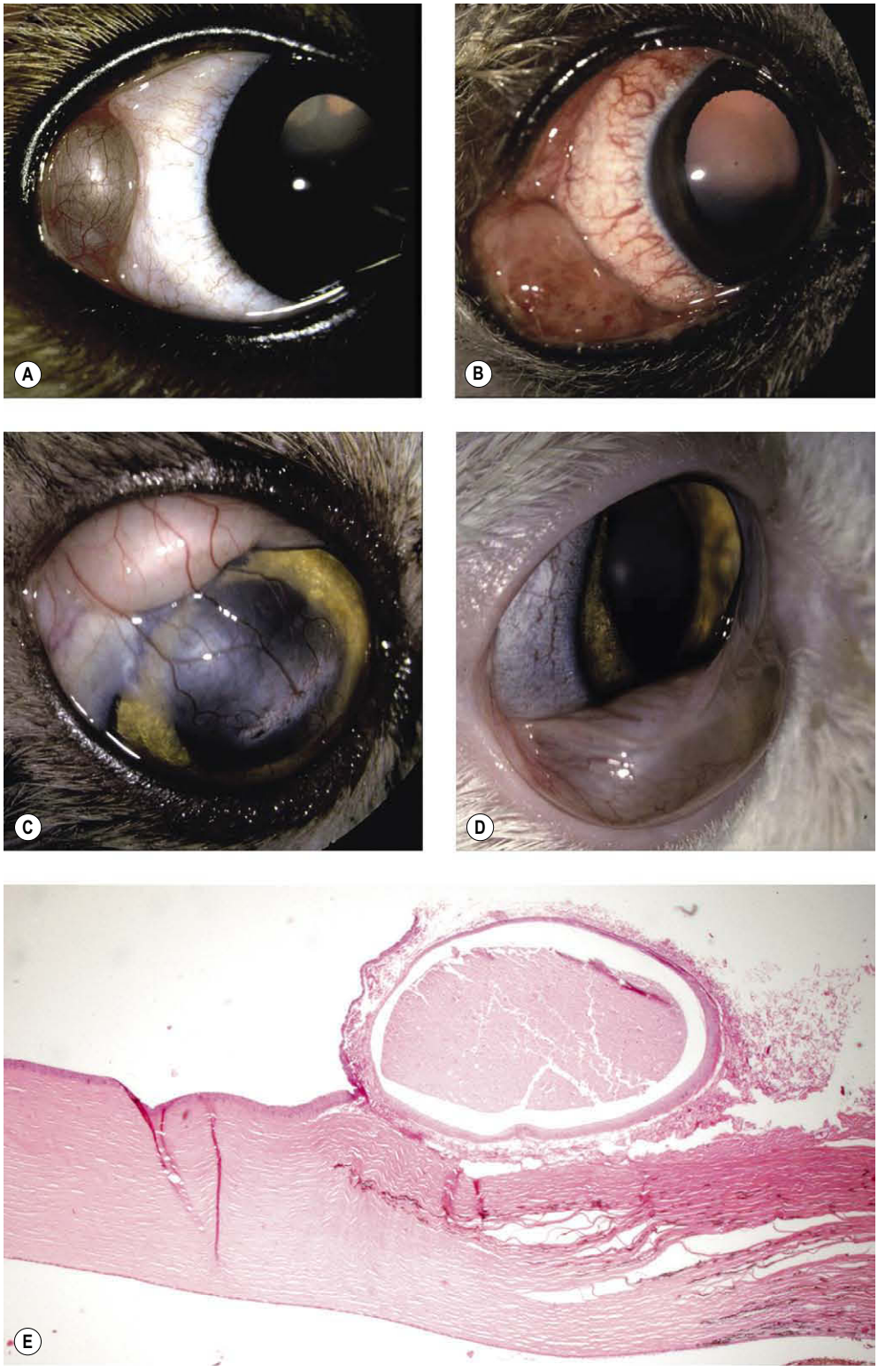


Figure 7.62 Conjunctival inclusion cysts. (A) Goldendoodle, 6 months old: this temporal bulbar conjunctival cyst was present bilaterally. (B) Bichon Frise, 9 years old: the inferior-temporal palpebral conjunctiva was involved. (C) Persian, 5 years old: the superior bulbar conjunctiva is involved. The cyst and adjacent corneal disease are from presumed FHV-1 infection. (D) DSH, 12 years old: a symblepharon resulted in a large cyst and the swelling of the lower palpebral conjunctiva. (E) Low magnification photomicrograph showing an epithelial cyst embedded in the substantia propria at the limbus.

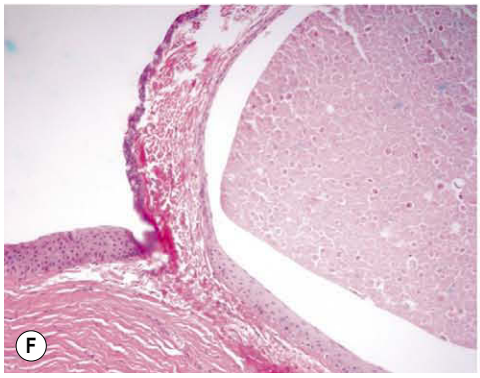
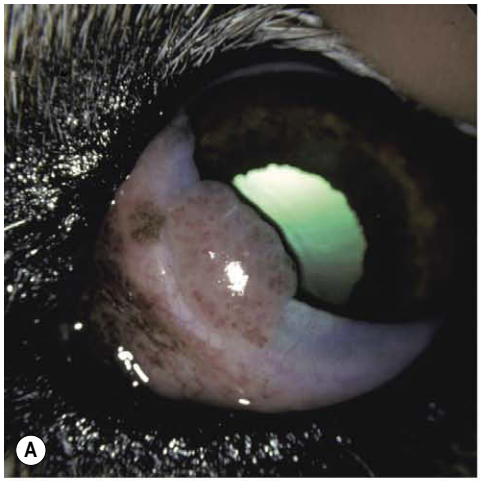
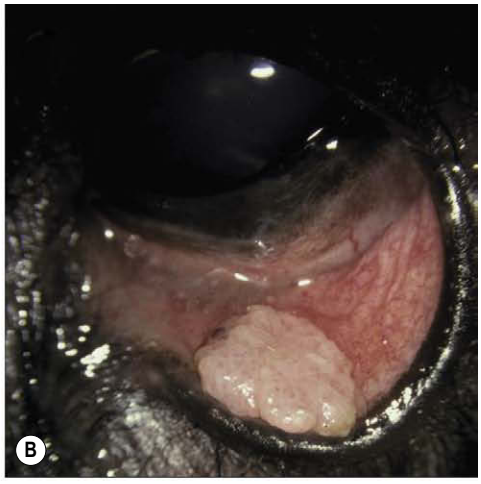


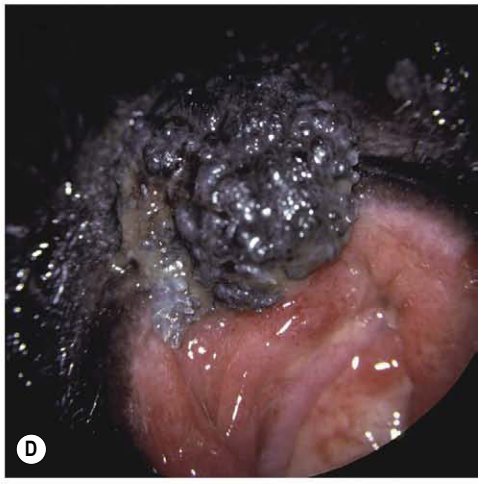


Figure 7.62, cont'd (F) Higher magnification of (E). (G) Photomicrograph of a similar cyst with thinner walls.









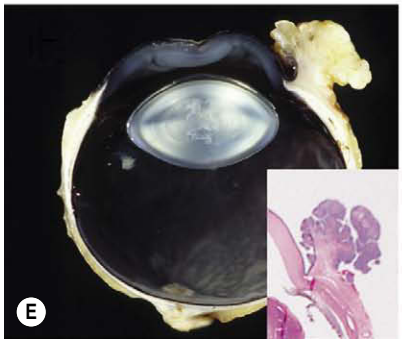






Figure 7.63 Conjunctival squamous papilloma or reactive papilloma. (A) Mixed Breed, 7 years old: a non-pigmented papilloma extends from the palpebral surface of the nictitans. (B) Poodle, 7 years old: the tumor originated from the lower palpebral conjunctiva. (C) Pembroke Welsh Corgi, 12 years old: this pigmented mass involved the lower palpebral conjunctiva and the lid margin. (D) Mixed Breed, 13 months old: this solitary pigmented tumor involved the superior palpebral conjunctiva and lid margin. (E) Gross photograph of a globe with a reactive papilloma on the conjunctiva. The inset shows the same lesion in a low magnification photomicrograph. (F,G) Low magnification photomicrographs showing the typical appearance of squamous papilloma. Delicate branching fronds are supported by a minimal vascular stroma.

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Chapter 8

Diseases of the cornea and sclera

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NORMAL CORNEAL ANATOMY

The tear film

- The normal tear film is not visible using standard histopathology techniques
- Functions of the tear film include:
  - Prevention of desiccation of the corneal epithelium and anterior stroma
  - Distribution of oxygen and nutrients consumed by the corneal epithelium and anterior stroma
  - Protection of the ocular surface:
    - By trapping and flushing away particulate foreign material
    - By immunoglobulins and other, non-specific anti-microbial proteins and peptides within the tear film, such as lysozyme and lactoferrin
    - By providing a medium by which inflammatory cells can gain access to the tissues of the anterior cornea
  - Provision of a glass-like smooth air-tissue interface that is essential for the optical clarity of the cornea
    - Allows effective light refraction and the formation of a high quality focused image on the retina
- The components of the tear film
  - The mucous layer
    - Secreted predominantly by conjunctival goblet cells, with lesser contributions by the Harderian gland where present, corneal and conjunctival epithelial cells
    - Attaches to the anterior surface of the corneal epithelium and adsorbs water, stabilizing the tear film
  - The aqueous layer
    - Secreted by the lacrimal gland, the nictitans gland and dispersed lacrimal glandular tissue in the conjunctival fornix
    - The aqueous component of the tear film is the vehicle for delivery of oxygen and nutrients to the anterior cornea
  - The lipid layer
    - Secreted by the tarsal (meibomian) glands at the lid margin
    - Forms an outer layer which slows evaporation and allows the even spread of the tear film over the ocular surface.

The corneal epithelium (Fig. 8.1)

Functions

- A physical barrier excluding pathogenic organisms
  - The corneal epithelium is capable of rapid response to injury, covering an epithelial deficit by a process of relaxation of intercellular connections and vigorous cellular migration
- A lipophilic barrier to the absorption of hydrophilic substances
  - This is the principle behind the use of the hydrophilic dye, fluorescein to detect defects in corneal epithelial integrity (corneal ulceration)
- The afferent branch of the corneal blink reflex
  - Unsheathed nerve endings are distributed within the corneal epithelium
- The contribution of the cornea to the maintenance of immune privilege in the eye, and to the inhibition of neovascular proliferation within the corneal stroma.

Components

Squamous cells

- Two or three superficial layers of non-keratinized cells
- Microvillae/microplicae present on these cells are postulated to help 'anchor' the tear film to the corneal surface
- The number of layers of this cell type is increased in larger species, e.g. ungulates and in species whose eyes maintain function underwater.

Wing cells

- Two or three layers of polyhedral cells
- The number of layers of this cell type is increased in larger species, e.g. ungulates and in species whose eyes maintain function underwater.

Basal cells

- A single layer of columnar cells, attached to the basal lamina by hemidesmosomes and to neighboring cells by desmosomes
- Hemidesmosomes attach to anchoring fibrils in the basal lamina
- The basal cell layer rests flat on the basal lamina with no undulation in contrast to most of the surface epidermis.

The corneal epithelial basal lamina and the superficial stroma

The basal lamina of the corneal epithelium and the superficial stroma are structures that play an important role in corneal wound healing and several disease processes that will discussed later in this chapter.

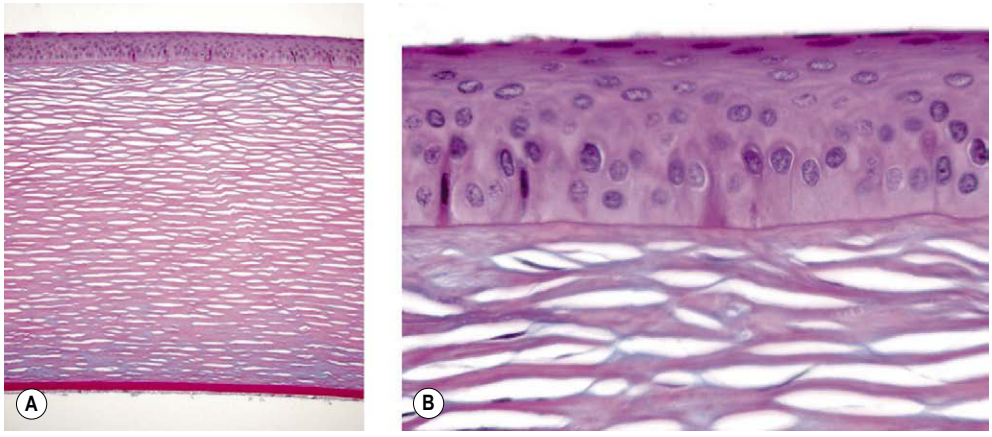


Figure 8.1 Normal cornea. (A) Low magnification photomicrograph showing a normal canine cornea (Alcian blue PAS stain). (B) Photomicrograph of the normal corneal epithelium and superficial stroma.

Key components of the basal lamina and superficial stroma include:

- Type IV collagen, laminin and fibronectin
- The superficial stroma differs from the lamellar stroma in that it is made up of a thin, acellular zone with tangled collagen into which the basal lamina anchors
  - This layer is analogous to Bowman's layer of the primate cornea and the corneas of cetaceans, elephants and several species of bird.

The lamellar corneal stroma

Functions of the lamellar stroma are:

- The maintenance of structural integrity, rigidity and the precise curvature of the globe
  - The rigidity of the globe is essential to maintain precisely defined physical properties that are required to focus light on the retina. This rigidity relies on the tensile properties of the collagenous corneal stroma and the sclera, and on the maintenance of a physiologically high intraocular pressure
  - The cornea represents a major refractive interface of the eye, and any changes in its curvature or thickness will impact the focusing of light on the retina
- Optical clarity
  - The optical clarity of the corneal stroma is dependant on the maintenance of a strict, orderly structural relationship between cells, collagen, and inter-cellular, glycosaminoglycans within a relatively dehydrated extra-cellular environment
    - Loss of optical clarity occurs if there is a failure to maintain relative dehydration of the corneal stroma, as occurs with loss of epithelial barrier function, vascular leakage, or particularly with loss of endothelial function (as discussed below)
  - The corneal stroma is an immune privileged tissue and it is avascular
    - Loss of optical clarity occurs with even slight inflammation or vascularization.

Descemet's membrane (Fig. 8.2)

Descemet's membrane is the basal lamina of the corneal endothelium. It forms a thick smooth membrane with elastic properties in terrestrial mammals but it is very thin in pinnipeds, birds, and reptiles.

Corneal endothelium

- The key function of the corneal endothelium is to maintain the stroma in a state of relative dehydration
  - The endothelium is a physical barrier to the movement of water into the corneal stroma from the anterior chamber
  - The endothelium functions to actively pump water out of the corneal stroma into the anterior chamber against a pressure gradient
- The endothelium is a monolayer of polygonal cells lining the posterior cornea
- In most adult animals, the endothelium has a very limited ability to proliferate in response to cell loss. However, metaplasia into spindle cells, movement along a surface, repair of the endothelium may occur. Damage to the endothelium might also be a stimulus for collagen matrix production of duplication of the Descemet's membrane.

Comparative Comments

- Although there is variation in the proteins and lipids, the functions and dynamics of the tear film are similar in humans and animal species. Indeed, rabbits and cats represent major experimental models used to study tear dynamics and deficiencies, relevant to humans
- There are close similarities between the anatomy and histology of the human cornea with the description given for other species. Bowman's layer is seen in the primate cornea and in certain avian corneas but is not seen as a distinct layer in most of the domestic mammalian species.

CONGENITAL AND HEREDITARY ABNORMALITIES

Congenital abnormalities in corneal size and shape

Microcornea: abnormally small cornea

Often seen with microphthalmos (see Ch. 3)

Cornea globosa in Rocky Mountain horses (Fig. 8.3)

Cornea globosa has been reported in association with congenital ocular anomalies in the Rocky Mountain horse. In some affected horses the radius of curvature of the cornea appears to be shortened, leading to excessive anterior curvature and protrusion of the cornea. These horses have abnormally deep anterior chambers. Other features of this inherited complex of multiple ocular abnormalities are discussed in detail in Chapter 3.

Keratoconus, conical distortion of the anterior corneal curvature

Although animals will occasionally have corneal malformation with physical features of keratoconus, there are no documented animal models with equivalent morphology to this common human disease

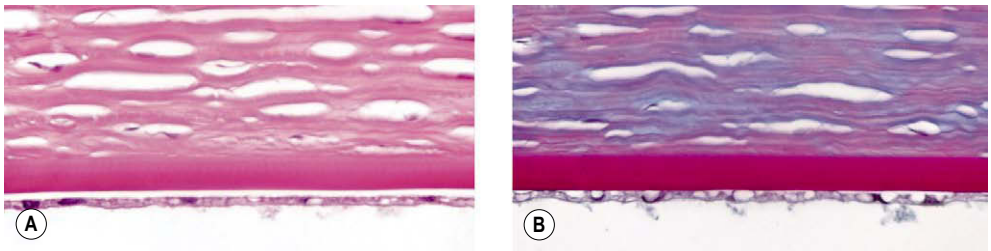


Figure 8.2 Normal posterior cornea. (A,B) Photomicrographs showing the normal posterior canine cornea (A, H&E; B, PAS).

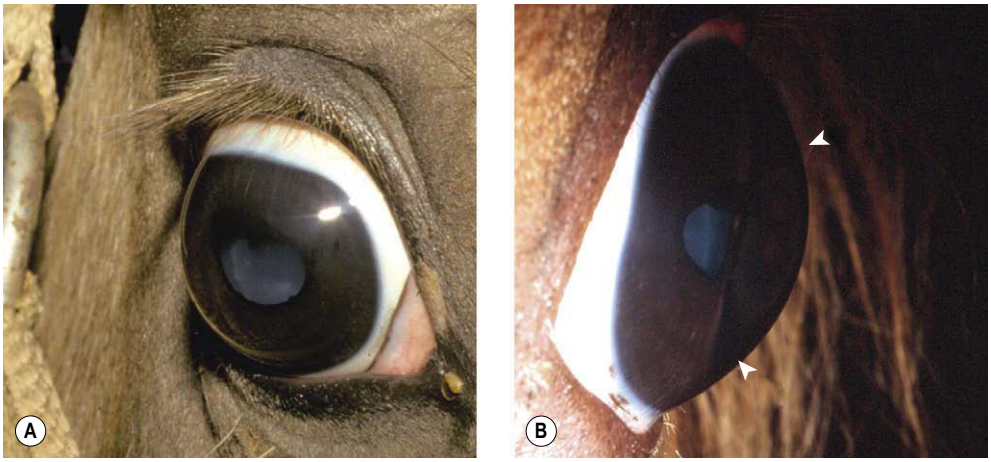


Figure 8.3 Rocky Mountain horse. (A) The right globe has a megalocornea and a diffuse cortical cataract. (B) A lateral view illustrates the increased corneal curvature (arrows) in addition to the enlarged cornea, i.e. cornea globosa.

- This difference in disease occurrence between species is likely due, at least in part, to the fact that the human disease involves breaks in Bowman's layer, which is absent or ill-defined in domestic animals.

Congenital corneal opacities

Peter's anomaly (see also Ch. 3)

In this complex congenital abnormality, focal corneal opacity is caused by the attachment of uveal tissue within the posterior cornea, and associated defect in Descemet's membrane (i.e. adherent leukoma). Attachments between the iris and cornea in dogs are also often referred to as persistent pupillary membrane but Peter's anomaly is more accurate.

Dermoid (see also Ch. 7)

A congenital, focal lesion (choristoma), in which corneal tissue is replaced by fully differentiated tissue of another sort, typically skin.

Comparative Comments

- With regard to congenital and hereditary abnormalities, megalocornea is inherited as an X-linked recessive in humans, frequently as an isolated bilateral abnormality
- Congenital corneal opacities may result from anterior cleavage anomalies and may be associated with abnormalities of the iridocorneal angle and iris
- Other significant congenital anomalies that occur in man are congenital hereditary endothelial dystrophy, causing bilateral congenital corneal edema; posterior keratoconus, a central indentation of the posterior cornea; congenital corneal staphyloma, characterized by ectasia of part or all of the cornea; and sclerocornea, an abnormality resulting in bilateral opacification and vascularization of the cornea, leading to its resembling the adjacent sclera
- Keratoconus in humans is characterized in its early stages by focal disruptions of the epithelial basement membrane and Bowman's layer, with subsequent bilateral central ectasia of the cornea
- Dermoids are congenital fibrovascular masses present within the cornea. They are believed to be caused by a failure of surface ectoderm to differentiate into normal corneal epithelium.

CORNEAL DYSTROPHIES AND DEGENERATIONS

Corneal epithelial dystrophies (Fig. 8.4)

Examples of corneal epithelial dystrophies in animals

- Corneal dystrophies are typically bilateral in presentation and a familial or breed predisposition is often documented or suspected
- Breed-related epithelial dystrophies are reported in dogs, these include:
  - Superficial punctate keratopathy in the Shetland Sheepdog and Long Haired Dachshund
    - Onset is typically in early adulthood, with varying progression throughout life. Affected animals typically present with multi-focal epithelial defects that lend an 'orange peel' appearance to the corneal surface, and are associated with small, round to annular opacities
    - The cause of these lesions is poorly understood – although some consider this to represent a primary epithelial dystrophy, qualitative tear film disease and immune-mediated keratitis have also been proposed as underlying abnormalities in affected dogs
- Morphologic features reported in eyes affected by epithelial dystrophy include:
  - Focal dysplasia of the basal lamina of the corneal epithelium
  - Dyskeratosis and necrosis of corneal epithelial cells
- In the COPLOW collection, however, there are only two examples of corneal epithelial dystrophies and none in dogs
  - One in a Basilisk lizard and one in a horse.

Corneal stromal dystrophies and degeneration

Because penetrating keratoplasty is performed so often in humans, there is a much greater understanding of the pathologic basis of human corneal dystrophies. In contrast, corneal tissues from uncomplicated cases of suspected corneal dystrophy in domestic animals are seldom submitted to COPLOW.

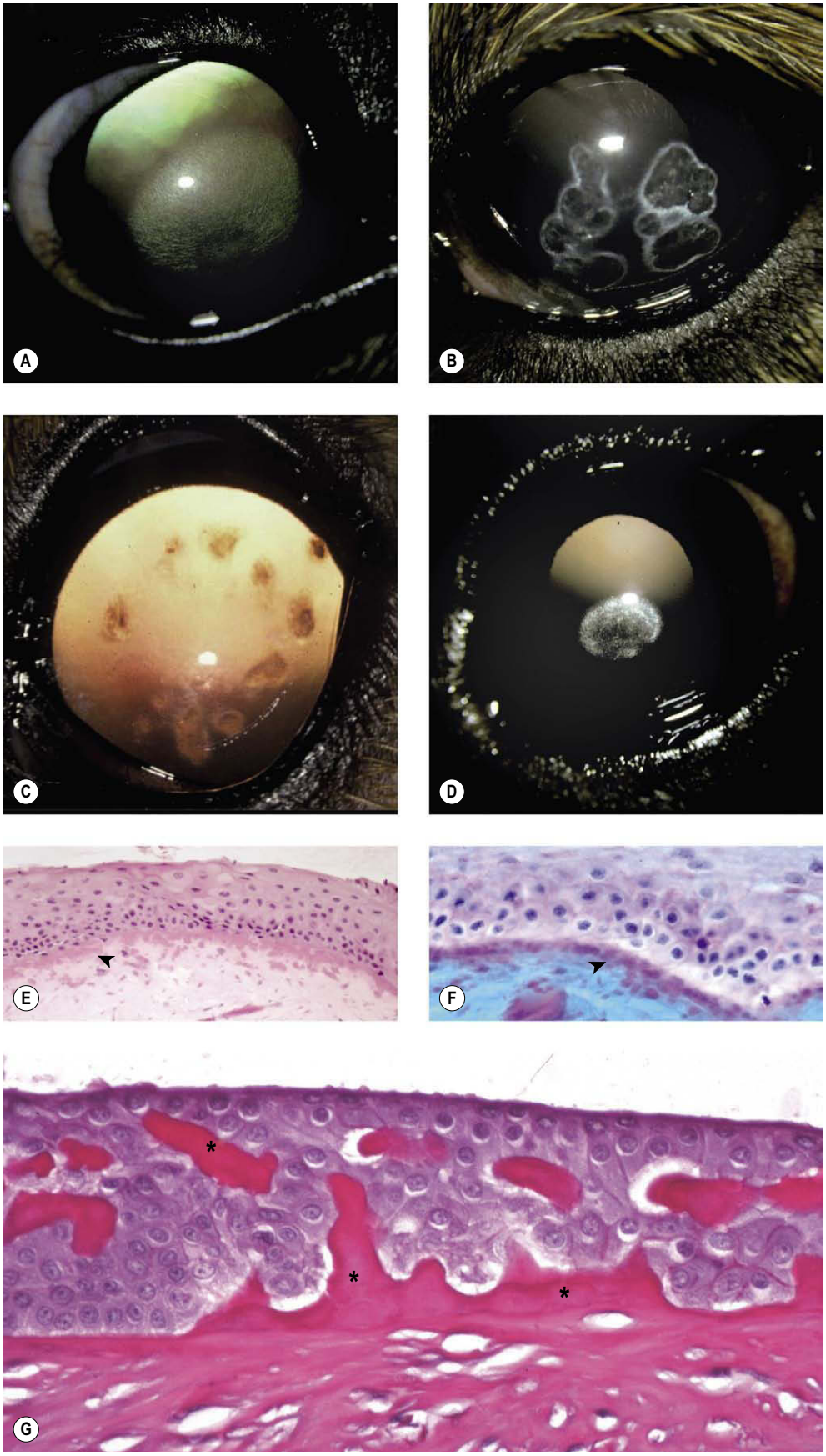


Figure 8.4 Epithelial dystrophy and stromal lipid dystrophy. (A) Afghan Hound, 3 years old: bilateral elliptical, superficial stromal dystrophy was present. (B) Shetland Sheepdog corneal dystrophy, 3.5 years old: multiple superficial facets with associated lipid deposits were present in both corneas. (C) Shetland Sheepdog, 2 years old: bilateral focal dystrophies can be seen by retroillumination. (D) Cavalier King Charles Spaniel, 4 years old: axial opacities were present bilaterally. (E,F) Photomicrographs of suspected corneal epithelial dystrophy in a horse showing marked irregularity in the corneal epithelial basal lamina (arrows) (E, H&E; F, Alcian blue PAS). (G) Photomicrograph showing the corneal epithelium and dysplastic basal lamina (*) from a Basilisk lizard (PAS stain).

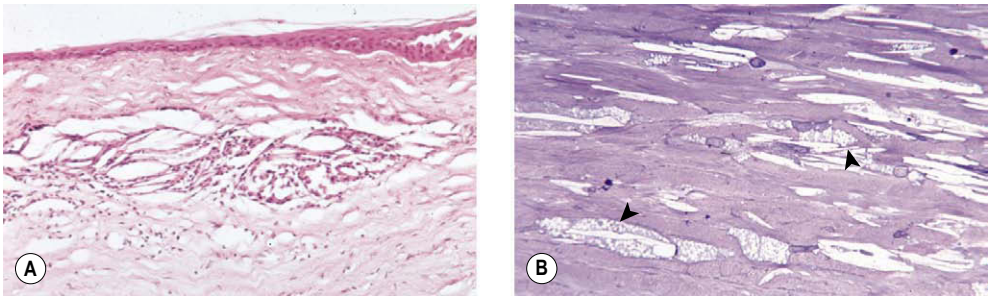


Figure 8.5 Cholesterol deposits, canine. (A) Photomicrograph showing a cholesterol granuloma in the midsuperficial stroma. (B) Photomicrograph showing keratocytes with vacuolated cytoplasm due to increased lipid content (arrows) (toluidine blue stain on 1 μm plastic section).

Lipid dystrophy, crystalline stromal dystrophy, corneal lipidosis (Fig. 8.5)

Several commonly occurring, breed-related corneal lipid dystrophy syndromes are reported in dogs. Although in some breeds, the inherited basis of corneal disease has been established and histopathological findings published, affected corneal tissues are seldom submitted to the pathology laboratory as they are neither painful nor vision-threatening in most cases.

In pathology submissions, lipid deposition in the cornea is usually found as a condition secondary to inflammation, or mass lesions involving the limbus and/or cornea.

Characteristics of lipid dystrophy which distinguish it from acquired disease include:

- Bilateral, generally relatively symmetrical, nature of disease
- Breed predisposition that includes the Siberian Husky, Beagle, Cavalier King Charles Spaniel, Collie, German Shepherd, Shetland Sheepdog, Afghan Hound and Airedale
- Found in an otherwise clear cornea:
  - Typically, there is no, or very limited, vascular in-growth and limited inflammatory response
- No defined relationship to underlying systemic metabolic disease
  - However, abnormalities in serum lipids and lipoproteins may affect the onset and progression of corneal opacities in dogs with primary corneal lipid dystrophies
  - Likely represents a primary abnormality in the metabolism of keratocytes.

Morphology of corneal lipid dystrophy

- The obvious lesion is free cholesterol between stromal lamellae, most often involving the anterior stroma. This is recognizable in paraffin-embedded sections as oblong spaces, including characteristic, needle-shaped, acicular clefts. Often lipid is evident within or surrounded by macrophage cells (cholesterol granuloma)
- Careful observation of surrounding keratocytes reveals that there are lipid vacuoles in the cytoplasm of keratocytes
- Lipid deposits whether intracellular or within the stroma will not be directly observable by standard paraffin histologic techniques because the lipid is dissolved in xylene and in paraffin during processing.

Acquired corneal lipid deposits (Fig. 8.6)

- Lipid keratopathy
  - Associated with vascularization of the cornea (that may be recognized prior to, or following, lipid deposition)
  - Lipid deposition may occur in the corneal stroma at the margins of localized proliferative diseases such as melanocytoma, nodular granulomatous episcleritis or focal trauma, or may be more diffuse when associated with keratitis or other generalized anterior segment inflammation (scleritis, uveitis)
  - There may, or may not, be an association with abnormal systemic lipid metabolism, such as endocrine disorders or excessive amounts of dietary lipids
- Arcus lipoides corneae
  - Originates near the limbus
  - Bilateral
  - Initially corneal blood vessels are absent, but vascularization is a subsequent response to the presence of lipid and typically is accompanied by the presence of lipid-filled macrophages. Indeed, the extent of vascularization and inflammation can modify further lipid deposition or removal
  - No causal association with local proliferative and inflammatory corneal disease
  - Associated with systemic metabolic diseases, such as hypothyroidism
  - In domestic and laboratory rabbits, feeding of diets high in cholesterol, or genetic hyperlipidemia ('Watanabe' rabbits), has been associated with lipid infiltration of the cornea (lipid keratopathy, arcus) as well as in other ocular tissues
    - A distinct form of anterior corneal (epithelial and epithelial basement membrane) dystrophy has also been reported in Dutch Belted rabbits
  - An association between serum lipids and corneal lipid deposition has also been widely recognized in captive tree frogs.

Mineral stromal dystrophy and degeneration (Fig. 8.7)

As with lipid, mineralization of the corneal stroma is most often encountered as a secondary process within our pathology collection. However, there are a few submissions with mineralization of the stroma in which there is either no underlying inflammation evident, or the degree of mineralization appears excessive relative to the limited inflammation present.

Corneal stromal mineralization in horses

- This presents as distinct areas of superficial corneal opacity
- The mineralization is confined to the superficial stroma, with minimal or no inflammation present
- Cases from the COPLOW collection do not have a history of metabolic disease and there is no obvious relationship to diet or to any particular breed or age.

Band keratopathy (Fig. 8.8)

- Band keratopathy represents a nonspecific degenerative process, and is named for its appearance as an approximately axial, horizontal band that lies within the inter-palpebral fissure

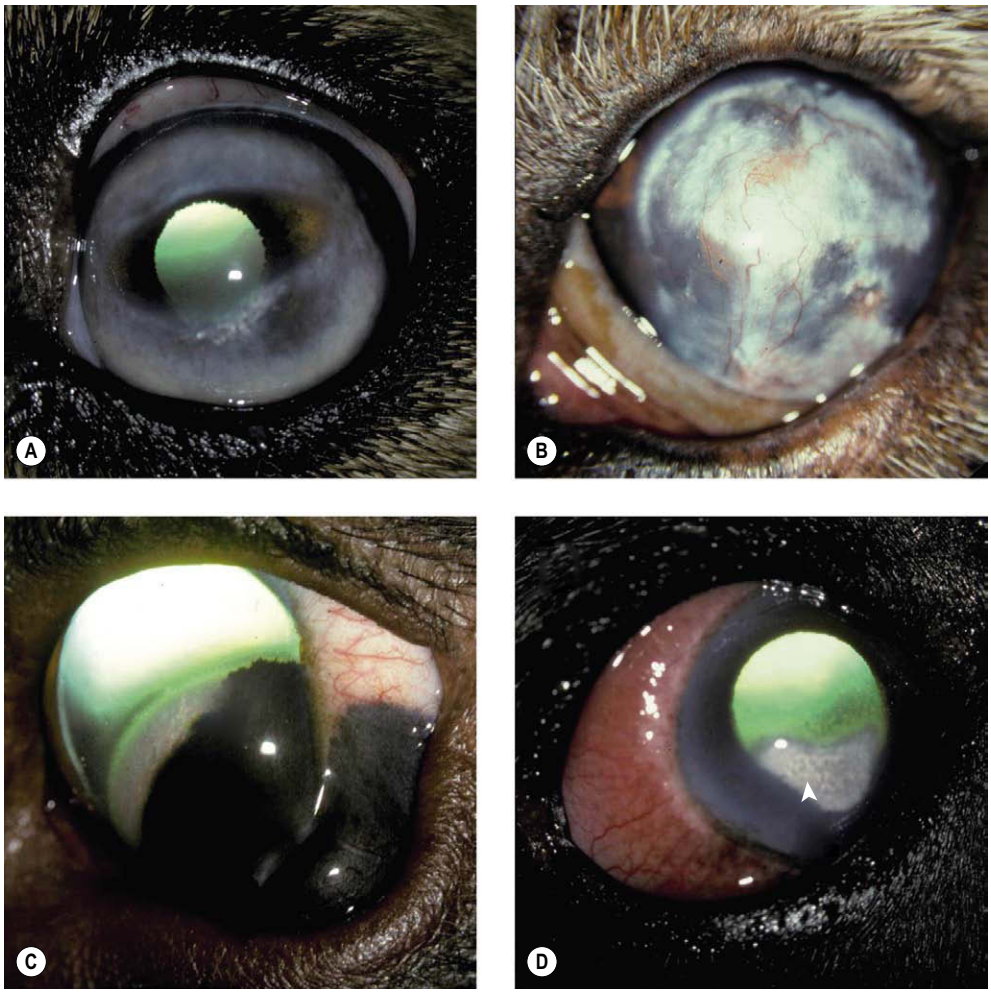


Figure 8.6 Lipid keratopathy and corneal fatty degeneration, clinical. (A) Golden Retriever cross, 3 years old: episcleritis and hypothyroidism resulted in this bilateral condition. (B) Golden Retriever, 4 years old: blood vessels are present at the limbus around this dense lipid deposit. (C) Labrador Retriever, 4 years old: the corneal lipid is at the advancing margin of the scleral shelf melanoma. (D) Rottweiler, 4 years old: diffuse scleritis, limbal edema and corneal vascularization are associated with the lipidosis (arrow).

- Band keratopathy is a common degenerative change observed in myriad ocular diseases, ranging from corneal scars to chronic / recurrent uveitis and phthisis bulbi (dystrophic calcification)
- Band keratopathy may also be seen in animals that have underlying disease leading to hypercalcemia (metastatic calcification)
- Corneal calcification has also been reported following topical therapy with steroid-phosphate preparations
- Morphologic characteristics
  - Superficial corneal stromal mineralization or basal laminar mineralization
  - The mineralized segment often becomes separated from the epithelium because the cornea continues to grow and surround the mineralized fragment, which remains as a linear, mineralized tissue fragment embedded in the anterior stroma.
  - Because the mineralized tissue was originally basal lamina, the remnant fragments stain positively with PAS.

Calcareous corneal degeneration, in aged dogs

- Slowly progressive disease
- Ultimately bilateral although not necessarily symmetrical in onset
- The diseased stroma displays white deposits that are gritty in texture
- Can progress to deep stromal ulcers or even corneal perforation
- Segmental mineralization of epithelial basal lamina (band keratopathy) and mineralization of the deeper stroma
- Affected animals may have no history of underlying ocular disease or evidence of systemic hypercalcemia.

Comparative Comments

Dystrophies of the cornea are defined as primary, inherited bilateral disorders and are classified according to the layer of the cornea most involved. These have been described, classified, and studied more fully in man than in other species.

- Although Cogan's microcystic or map-dot-fingerprint dystrophy is probably the most common, specimens are rarely received in the eye pathology laboratory
  - The chief histopathologic findings are a thickened basement membrane that extends into the epithelium, with associated abnormal epithelial cells and microcysts
- Lipid dystrophy was discussed among the corneal stromal dystrophies in nonhuman species
  - In man, the most common form of lipid deposit seen is arcus senilis, which is a primary condition
  - In Schnyder's crystalline dystrophy, a rare primary lipoidal degeneration, cholesterol crystals are noted within keratocytes and adjacent stroma

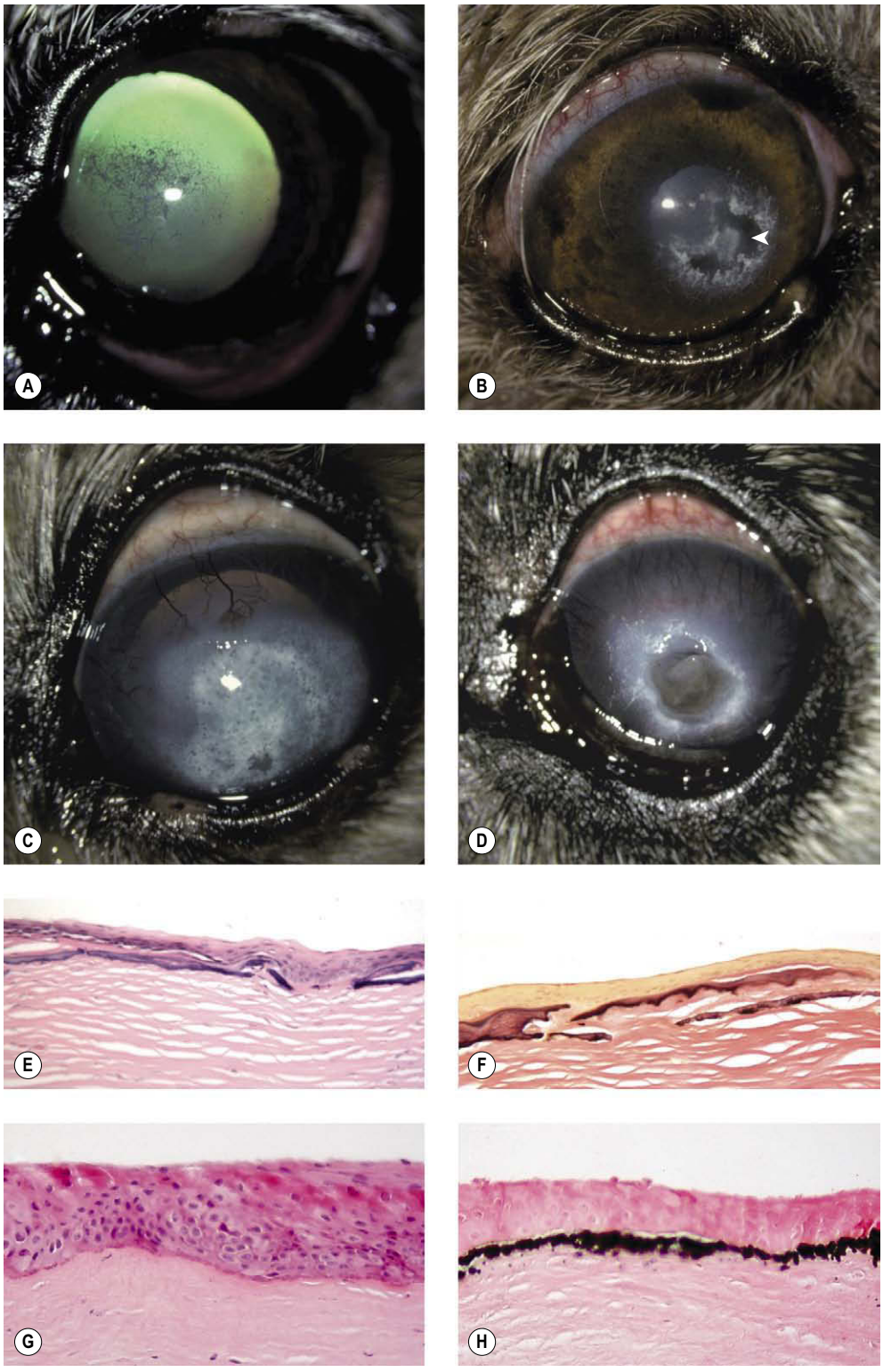


Figure 8.7 Corneal mineralization. (A) Miniature Dachshund, 11 years old: this is an early case with no vessels associated with the calcium deposit visible by retroillumination. (B) Cockapoo, 15 years old: the arrow points to a deep stromal crater within the calcium deposits. (C) Yorkshire Terrier, 16 years old: there is a large area of mineralization with corneal vessels superior. (D) Terrier mix, 13 years old: a central descemetocele is present with corneal vessels 360°. (E,F) Photomicrographs of canine corneal epithelium showing mineralization of the basal lamina and superficial stroma (band keratopathy) (E, H&E; F, elastin stain). (G) Photomicrograph of an equine corneal epithelium showing mineralization of the basal lamina. (H) This equine corneal epithelium shows marked mineral in the basal lamina and superficial stroma (von Kossa stain).

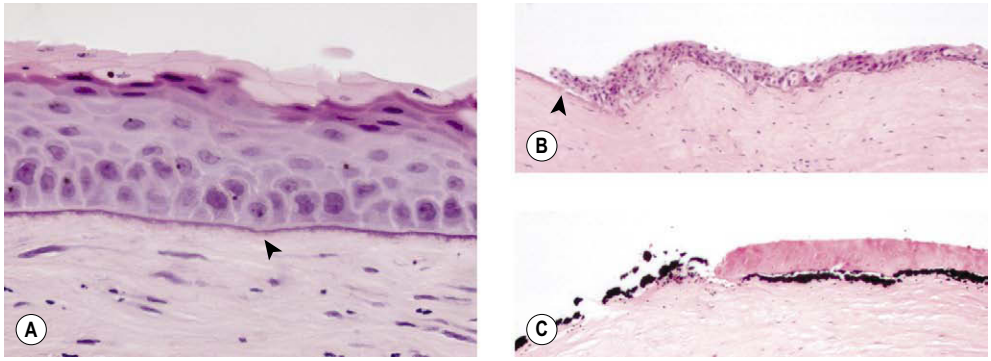


Figure 8.8 Band keratopathy. (A) Photomicrograph of a canine anterior cornea showing thickening and basophilia of the epithelial basal lamina typical of the mineralization seen in band keratopathy (arrow). (B) Photomicrograph of a canine anterior cornea showing mineralized basal lamina in an area of epithelial loss (arrow). (C) The mineralized basal lamina and anterior stroma in a dog cornea stain black with von Kossa stain.

Comparative Comments (continued)

- Also cholesterol and neutral fats are sometimes found as secondary lipid deposits following corneal inflammatory disease with new blood vessel formation
- The major human stromal dystrophies are:
  - Granular dystrophy, in which keratohyaline deposits are noted
  - Lattice dystrophy, in which fine-branching amyloid opacities are seen
  - Avellino dystrophy (combined granular/lattice dystrophy)
  - Macular dystrophy, in which there is proteoglycan deposition in all layers of the cornea except the epithelium
- Band keratopathy in humans conforms in appearance to the descriptions given here for other species
  - Band keratopathy may follow any chronic local corneal disease or occur in association with systemic hypercalcemic states and in eyes with longstanding chronic inflammation.

Corneal endothelial dystrophies and degeneration (Fig. 8.9)

As with the other corneal dystrophies, it can be difficult to distinguish true endothelial dystrophy from acquired endothelial disease, which is much more commonly encountered. There are, however, several canine examples of endothelial dystrophy in the COPLOW collection.

- Endothelial dystrophy with multifocal defects in Descemet's membrane in dogs less than 6 months old
  - There are three such cases with bilateral disease in the COPLOW collection in three different breeds
  - Euthanasia was elected in all three cases because of the severe, blinding nature of the corneal disease
  - The affected corneas were markedly thickened and opaque
  - Histopathology shows a relatively normal endothelium, but with multiple defects in Descemet's membrane. Within these defective areas, endothelial cells may be seen to 'colonize' the posterior stroma
- Breed related corneal endothelial dystrophy and spontaneous corneal endothelial degeneration (attenuation)
  - Boston Terriers and Chihuahuas are known to have a breed-related corneal endothelial dystrophy
  - Mature adult dogs are typically presented with bilateral corneal edema that begins temporally and progresses to involve the entire cornea. Secondary corneal ulceration, due to rupture of epithelial bullae, is a common complication of profound corneal edema
  - Affected dogs have corneal stromal edema and endothelial cell attenuation as a primary disease, without an identifiable underlying pathogenic mechanism
  - In the COPLOW collection there are 12 cases which are considered to represent breed-related corneal endothelial dystrophy
    - Five Boston Terriers, three Chihuahuas, three Puli, and one Poodle
  - In all cases, the only morphologic finding was corneal endothelial cell attenuation, with profound corneal stromal edema and no apparent reason for the endothelial cell degeneration.

Comparative Comments

The endothelial dystrophies in humans appear different from those described above in young dogs. In man, the endothelial dystrophies have three factors in common:

1. The endothelial cells become sparse and irregular.
2. The abnormal endothelial cells produce excess collagen posterior to Descemet's membrane, causing a multilaminar structure.
3. Excrescences form on Descemet's membrane.

The most common endothelial dystrophy in humans is Fuchs' dystrophy, which constitutes the common indication for corneal surgery for a corneal dystrophy.

Secondary degenerative endothelial diseases (Fig. 8.10)

Pathogenic mechanisms

- Postoperative/iatrogenic (see Ch. 4)
  - Corneal endothelial attenuation is not uncommon as a postoperative complication following intraocular surgery, most notably, cataract surgery
- Any other disease process associated with tissue contact with the corneal endothelium such as anterior synechiae, or uveal masses such as neoplasms or cysts
  - Inflammatory disease may also play a role in endothelial dysfunction in some of these disease processes
- Advanced age
  - Corneal endothelial density reduces progressively with age and may ultimately fall below a critical density that is needed to maintain relative dehydration of the corneal stroma

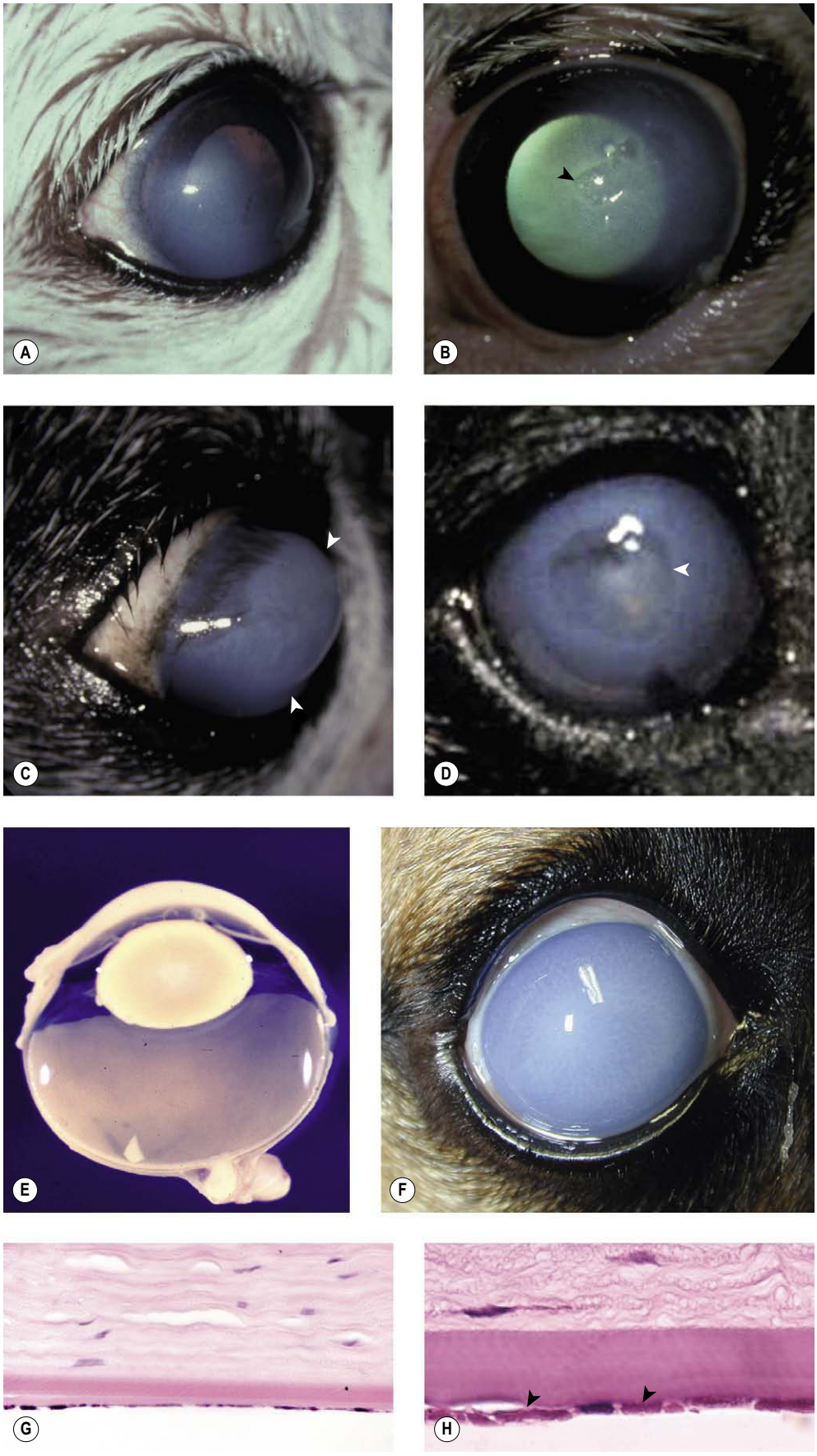


Figure 8.9 Corneal endothelial dystrophy. (A) Chihuahua, 10 years old: bilateral temporal edema was present. (B) Boston Terrier, 8 years old: the arrow points to epithelial bullae superficial to the stromal edema. (C) Boston Terrier, 7 years old: the arrows delineate the keratoconus resulting from severe corneal edema. (D) Dachshund, 11 years old: the arrow points to the edge of a deep corneal crater (facet), secondary to the edema and previous ulcer. (E) Gross photograph of a canine globe with endothelial dystrophy showing marked corneal stromal thickening. (F) Clinical photograph of a canine eye with dense corneal edema resulting in a blue to white opacity secondary to endothelial disease. (G,H) Photomicrographs showing the corneal endothelium of the eye in (E). The endothelium is attenuated and there are eosinophilic intracytoplasmic inclusions (arrows).

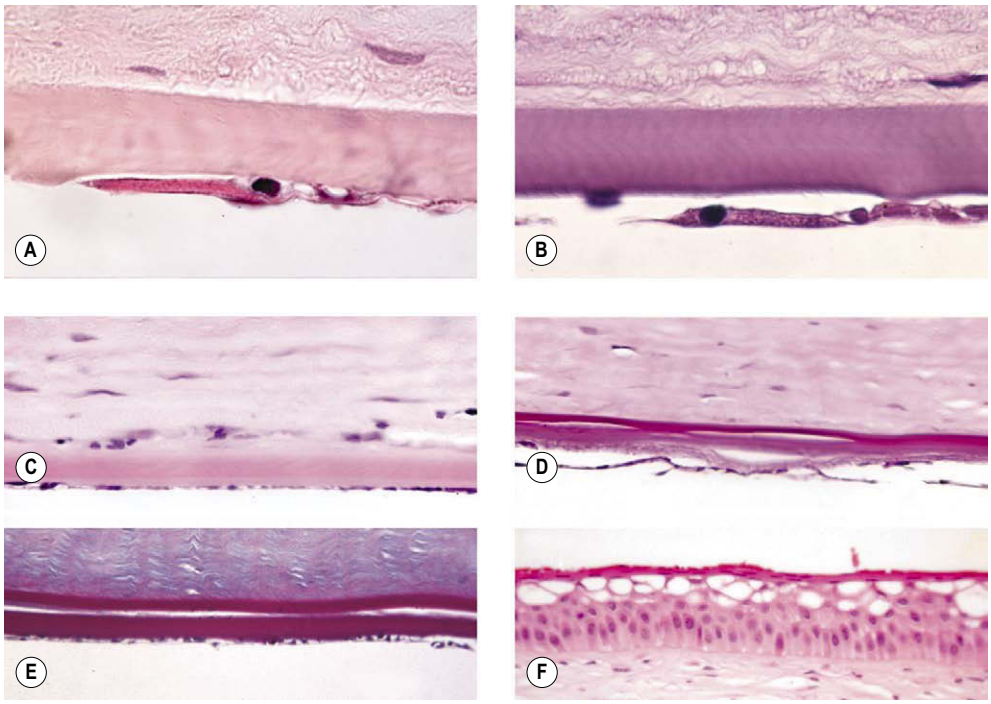


Figure 8.10 Corneal endothelial disease. (A,B) Photomicrographs of attenuated and abnormal corneal endothelium (B, PAS stain). (C) Photomicrograph showing attenuated corneal endothelium in a dog. (D) Retrocorneal membrane and doubling of Descemet's membrane in a dog cornea (PAS stain). (E) Prominent doubling of Descemet's membrane. (F) Corneal epithelium showing microvesicular change suggestive of corneal edema.

- Glaucoma
- Lens luxation
  - Focal edema due to direct contact between the displaced lens and corneal endothelium
  - Diffuse edema may be associated with secondary glaucoma.

Morphologic features of corneal endothelial degeneration

- The early changes are confined to endothelial attenuation, characterized by a reduction in cell density that is recognized as a 'spreading' of each individual endothelial cell, such that the distance between sampled nuclei is larger and the cell thickness is reduced
- Retrocorneal membrane formation
  - More advanced or longer standing cases demonstrate spindle cell metaplasia of the endothelium, with or without collagen formation
- Duplication of Descemet's membrane
  - This phenomenon is seen in dogs and cats, but not in horses, after intraocular surgery, blunt trauma, lens luxation and in other conditions where the endothelium might be 'stressed'
  - Descemet's is usually duplicated; with the new, posterior, Descemet's being approximately the same thickness as the original, anterior Descemet's membrane
  - The mechanism responsible for duplication of Descemet's membrane is unknown.

Severe corneal edema (corneal hydrops) associated with Descemet's membrane rupture (Figs 8.11, 8.12)

- Most of the examples of this condition in the COPLOW collection are in cats (five cats), although the condition has been reported in other species including horses
- The rapidity of onset is reflected in the other term for the condition, 'acute bullous keratopathy'
- The condition is characterized by rapidly developing, dense, relatively well-circumscribed corneal edema, with large coalescing bullae within the stroma and gross distortion of the corneal profile. Pronounced conical or globular forward protrusion of the anterior profile of the cornea ensues
- Histologically, rupture of Descemet's membrane is a consistent finding, and is associated with marked stromal edema with little or no inflammation.

CHRONIC KERATITIS, SUPERFICIAL

Chronic keratitis represents a non-specific end result of many diverse pathogenic pathways, including:

- Physical irritation from contact with hair, inflammatory or neoplastic masses, or airborne particulate material
- Desiccation caused by:
  - Exophthalmos or buphthalmos which impede eyelid closure and leads to inadequate distribution of the tear film
  - Inability to blink related to neurologic lesions affecting the facial nerve
  - Loss of corneal sensitivity related to lesions affecting the ophthalmic branch of the trigeminal nerve, with failure to initiate a protective blink or lacrimal response to irritation
  - Disorders resulting in decreased secretion of the aqueous component of tears
    - Chronic inflammation of the lacrimal and/or nictitans gland
    - Atrophy of these glands or obstruction of their ducts, secondary to trauma, inflammation, chemical injury, or radiation damage
    - Conjunctival xerosis or fibrosis
    - Neurogenic disease

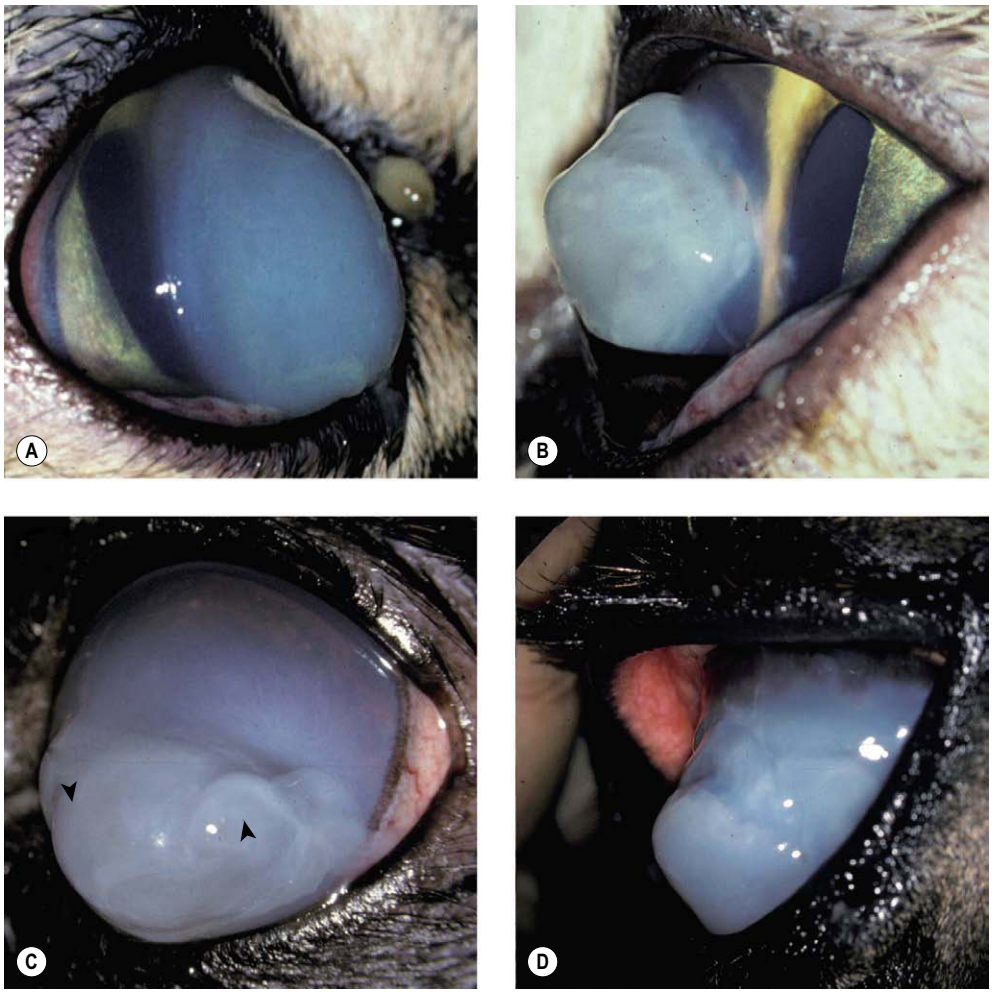


Figure 8.11 Corneal hydrops, clinical. (A) DSH, 1 year old: the lateral view shows the increased corneal curvature due to the severe edema. (B) DSH, 2.5 years old: the protruding cornea is irregular in contour. (C) Pomeranian, 5 years old: diffuse stromal edema is present with associated large epithelial bullae (arrows). (D) Thoroughbred, 3 years old: the acute edema caused the irregular conical cornea.

- Qualitative tear film disorders including:
  - Disorders of the conjunctiva resulting in inadequate mucin secretion
    - Chronic inflammation
    - Vitamin A deficiency, which causes squamous metaplasia with keratinization of mucus secreting epithelia
    - These disorders may also be associated with reduced secretion of aqueous tears
  - Disorders of the eyelid margin
    - Resulting in inadequate secretion of tear film lipid by tarsal/meibomian glands
- Recurrent episodes of corneal ulceration for whatever reason
- Keratitis due to specific corneal pathogens, e.g., Moraxella bovis, Feline herpesvirus-1
- Immune-mediated disease
  - The most commonly encountered breed-related condition being chronic superficial keratitis, previously known as pannus or Überreiter's syndrome, in dogs (see below).

Morphologic features of chronic keratitis (Fig. 8.13)

The epithelial response (epidermalization) is dependant on an intact limbal epithelium because the stem cells for the cornea reside only in the limbus. The components of the epithelial response in chronic superficial keratitis are:

- Hyperkeratosis
- Acanthosis
- Rete ridge formation
- Melanosis

The stromal response includes:

- Vascular in-growth from the limbus
- Reorganization of stromal collagen, with scarring
- Melanosis
- Inflammatory cell infiltration
  - Which depends on the stage of disease, prior therapy and the nature of the inflammation locally at the time of sampling

The basal lamina response:

- Marked thickening of the basal lamina may occur in response to repeated ulceration and re-epithelialization.

CHRONIC SUPERFICIAL KERATITIS (CSK, PREVIOUSLY TERMED PANNUS OR ÜBERREITER'S SYNDROME) (Fig. 8.14)

- This is a chronic, progressive, immune-mediated inflammatory condition which spreads from the limbus across the

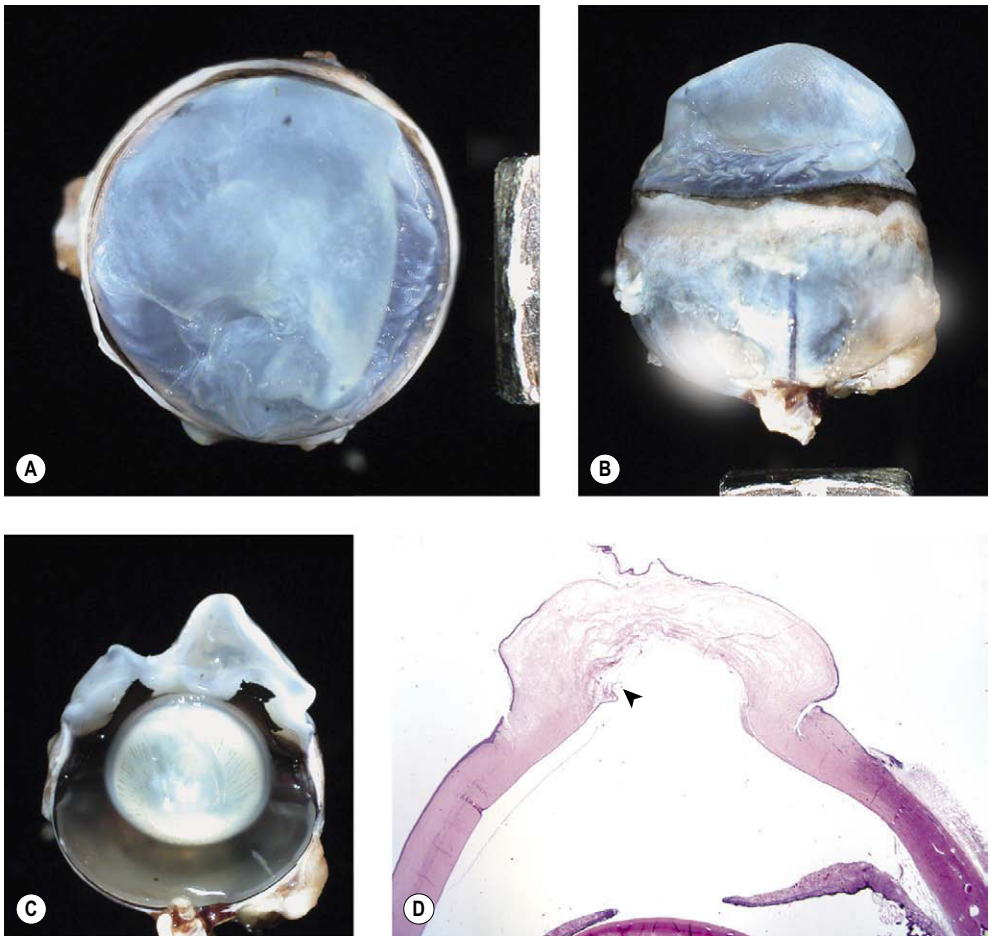


Figure 8.12 Feline corneal hydrops, pathology. (A–C) Three gross photographs of the same cat eye showing corneal hydrops and misshapen, markedly edematous corneal stroma. (D) Low magnification photomicrograph of the same cat eye showing edema, epithelial separation and a defect in Descemet's membrane (arrow).

superficial cornea, typically commencing in the temporal quadrant
- This bilateral condition has a predilection for the adult German Shepherd dog, Tervuren, Greyhound, Border Collie and Siberian Husky, although other breeds may be affected sporadically
- Ultraviolet light exposure has been implicated as a factor in the pathogenesis, and related environmental factors including altitude, sunlight exposure and dust may all adversely impact disease onset and severity.

Morphologic features of chronic superficial keratitis

- Lichenoid (interface) lymphoplasmacytic inflammation
- Superficial stromal fibrovascular proliferation and scarring, with subsequent melanosis
- Increased epithelial cell apoptosis
- Increased epithelial cell mitotic activity, but no associated epithelial erosion or ulceration.

The prognosis for achieving disease control and preserving vision may be poorer in those animals that show rapid onset of disease in early adulthood. However, most affected dogs show a favorable response to topical immunosuppressive therapy.

FELINE EOSINOPHILIC KERATITIS (PROLIFERATIVE KERATITIS) (Figs 8.15, 8.16)

Feline eosinophilic keratitis is a relatively commonly encountered disease in companion animal veterinary practice. However, the disease is under-represented in a pathology collection because it is usually diagnosed on the basis of clinical and/or cytological findings alone. There are only 24 cases in the COPLOW collection, most of which are keratectomy specimens.

- Feline eosinophilic keratitis typically extends across the limbus as a kerato-conjunctivitis. Eosinophilic conjunctivitis and eyelid margin erosive lesions may also be seen in the absence of significant corneal disease
- Lesions are most often unilateral, although bilateral involvement does occur
- Grossly the disease appears as a vascularized, peri-limbal, raised, proliferative lesion, with an irregular surface that has characteristic superficial plaques of white material. Although localized, corneal involvement can be extensive
- An association between eosinophilic keratitis and *Feline herpesvirus-1* infection has been demonstrated in some affected cats but virologic studies have not defined a consistent relationship between the presence of this virus and eosinophilic keratitis in all cases

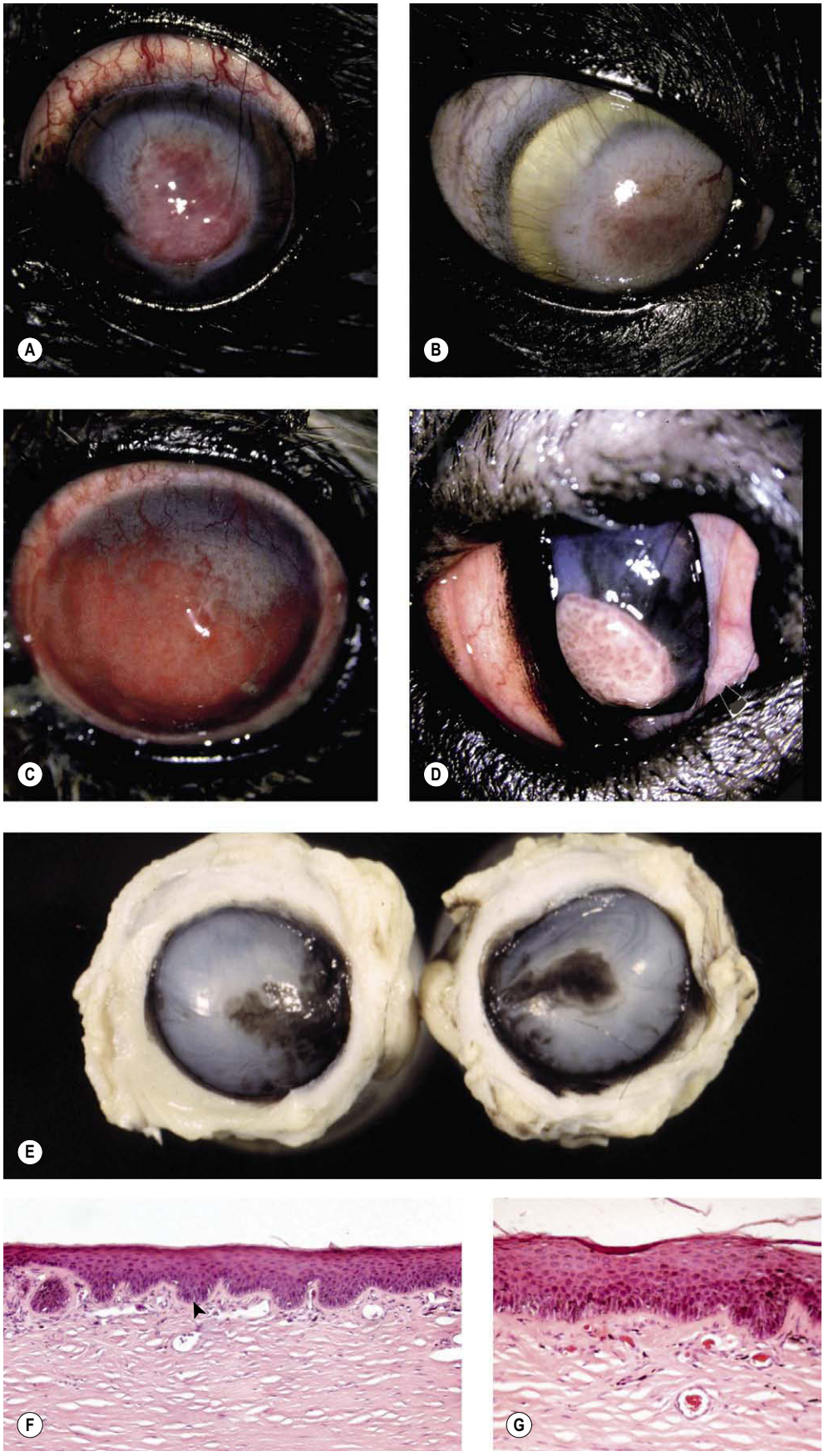


Figure 8.13 Superficial chronic keratitis. (A) Shih Tzu, 6 years old: this was the result of previous keratomalacia. (B) DSH, 7 years old: FHV-1 with secondary bacterial infection resolved but lead to the development of a dense fibrovascular scar. (C) Shih Tzu, 11 years old: poorly controlled dry eye syndrome led to severe chronic superficial keratitis. (D) Chinese Shar-Pei, 1 year old: this resulted from primary entropion. (E) Gross photograph of both globes from a Pug dog showing melanin pigment deposition in superficial chronic pigmentary keratitis. (F,G) Photomicrographs showing epithelial thickening, rete ridge formation (arrow), superficial stromal fibrosis and vascularization, and minimal lymphocytic infiltration in canine superficial chronic keratitis.

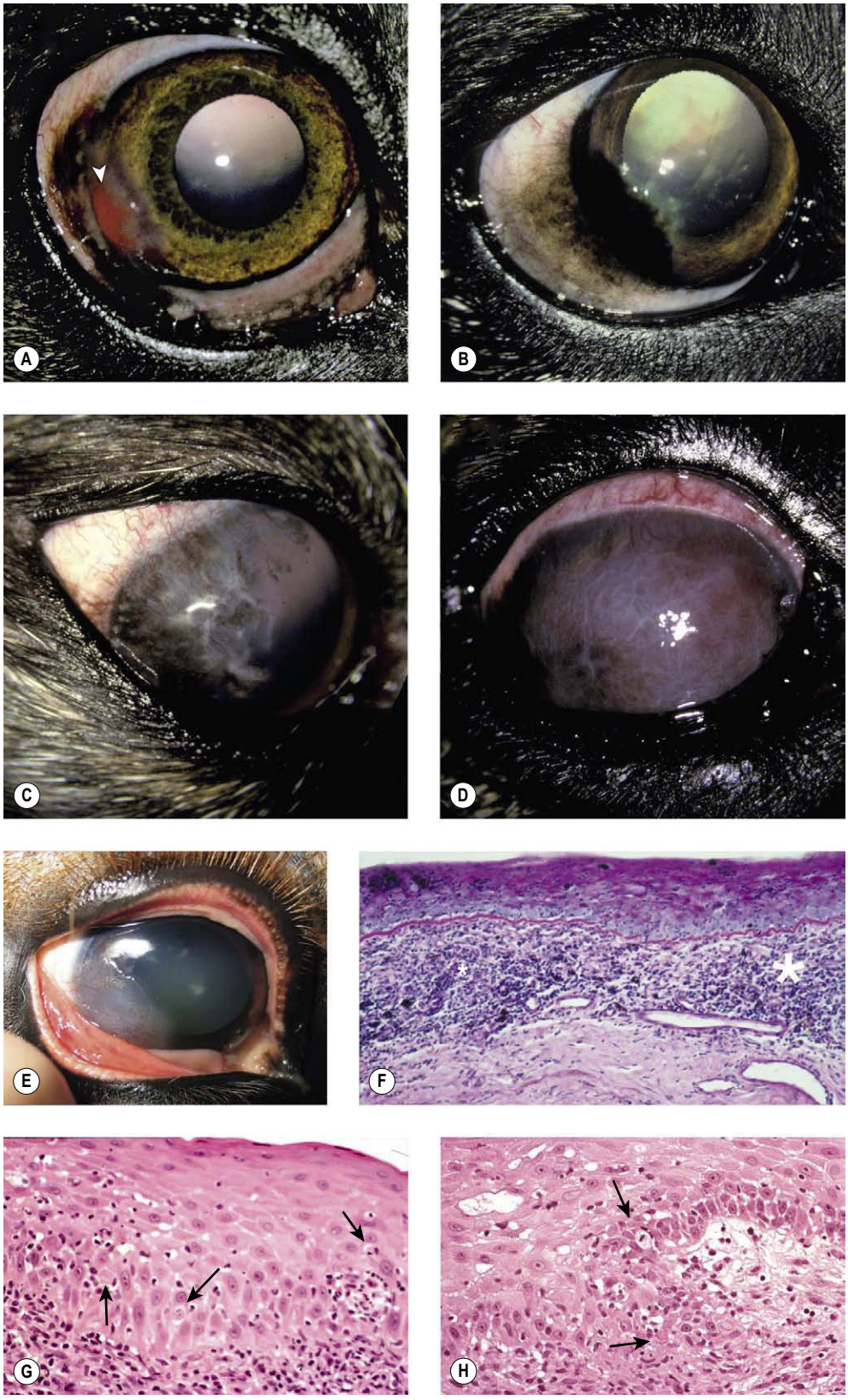


Figure 8.14 Canine chronic superficial keratitis (degenerative pannus). (A) German Shepherd Dog, 4 years old: the arrowhead points to the early temporal limbal vascularization. (B) Belgian Tervuren, 2 years old: temporal corneal pigment is the more remarkable finding in this right eye. (C) Greyhound, 4 years old: thin corneal vessels, lipid and pigment are present. (D) German Shepherd Dog, 6.5 years old: the entire cornea is vascularized in this advanced case. (E) Clinical photograph showing the superficial corneal proliferative reaction advancing over the temporal limbus. (F) Photomicrograph showing the typical interface inflammatory infiltrate (*). (G,H) Photomicrographs showing necrosis of individual epithelial cells typical of the disease (arrows).

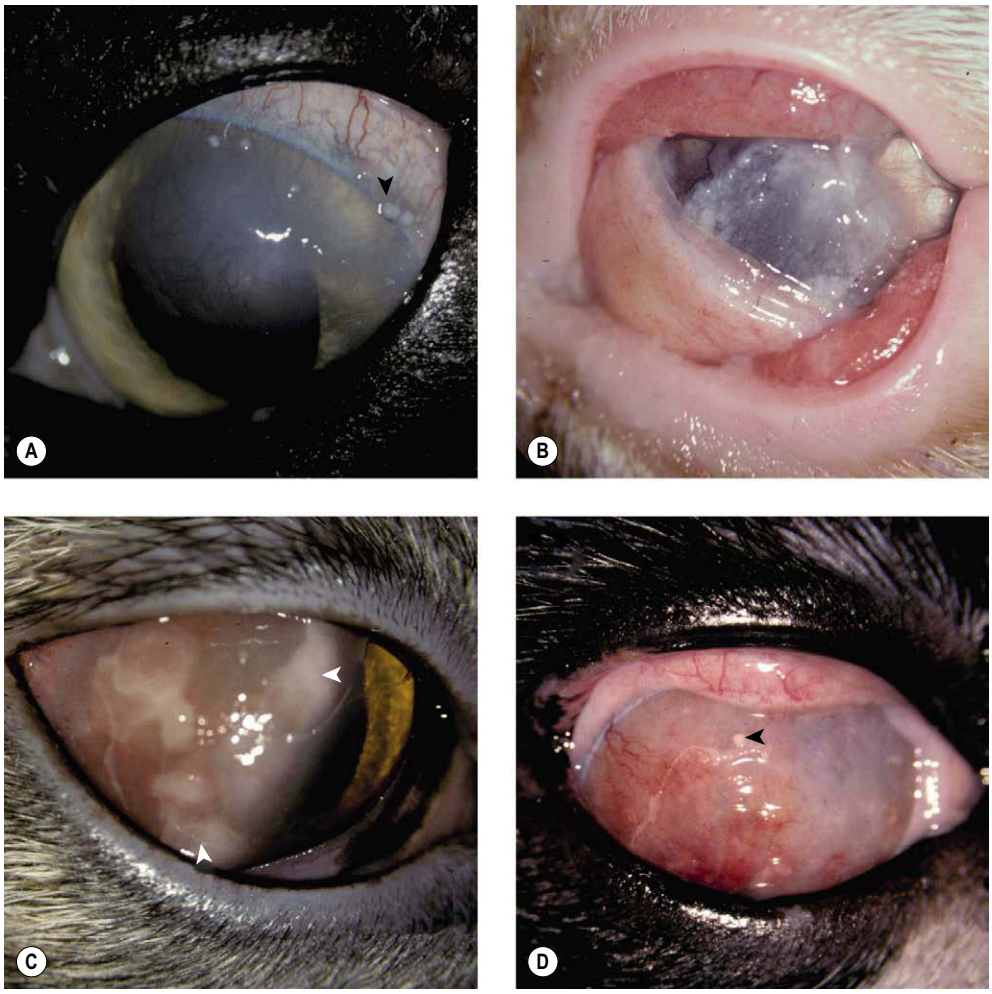


Figure 8.15 Feline eosinophilic keratitis, clinical. (A) DSH, 14 years old: the arrow points to one of the many superficial white plaques typical of the disease. (B) DSH, 4 years old: a thick, white, gritty plaque covers most of the cornea. (C) DSH, 1.5 years old: homogeneous white material (arrows) is present over the highly vascularized cornea. (D) DLH, 8 years old: the arrow points to a superficial white plaque on the vascularized cornea.

  - Roles for mycoplasma and novel *chlamydiae* in feline conjunctival and corneal disease have also been proposed, but have not yet been specifically evaluated in eosinophilic/proliferative keratitis
  - Eosinophilic/proliferative keratitis, and FHV-1 stromal keratitis likely represent similar immune-mediated disorders of the feline cornea, that may or may not share the same inciting factors
- Eosinophilic keratitis generally shows a dramatic response to topical immunosuppressive therapy
- Morphologic features of feline eosinophilic keratitis:
  - The epithelium is usually intact but, occasionally, an ulcerated surface may be lined by granular, acellular protein that likely represents granules liberated from eosinophils and/or mast cells. In addition to focal absence or thinning of the epithelium, hypertrophy and hyperplasia of the epithelium may also be seen
  - The normal superficial lamellar stroma may be completely effaced
  - Associated new corneal blood vessels can be large and may cross the lesion obliquely
  - The inflammatory infiltrate is lympho-plasmacytic with variable numbers of eosinophils and mast cells
    - Eosinophils often do not dominate the infiltrate and they may even be present in very small numbers.

EQUINE EOSINOPHILIC KERATITIS, EQUINE SUPERFICIAL CORNEAL SEQUESTRUM, OR EQUINE INDOLENT ULCER (Fig. 8.17)

These three conditions share similar clinical and morphologic features to an extent that, in the cases submitted to COPLOW, it has not been possible to distinguish one syndrome from another. There are 16 cases in the COPLOW collection, with clinical or morphologic features suggesting one or the other of these syndromes. However, samples are seldom submitted from cases with a clinical diagnosis of eosinophilic keratitis for histopathologic evaluation, because the diagnosis is frequently made by cytology.

- These conditions present as superficial recurrent or non-healing ulcers affecting the peripheral cornea
- Similar clinical and histopathological findings have been reported in horses with ocular onchocerciasis, in which microfilaria have been identified within the corneal or conjunctival tissues
- Morphologic features of the disease include:
  - A failure of epithelial attachment
  - A very thin hyper-eosinophilic band of material between the unattached epithelium and the more normal stroma

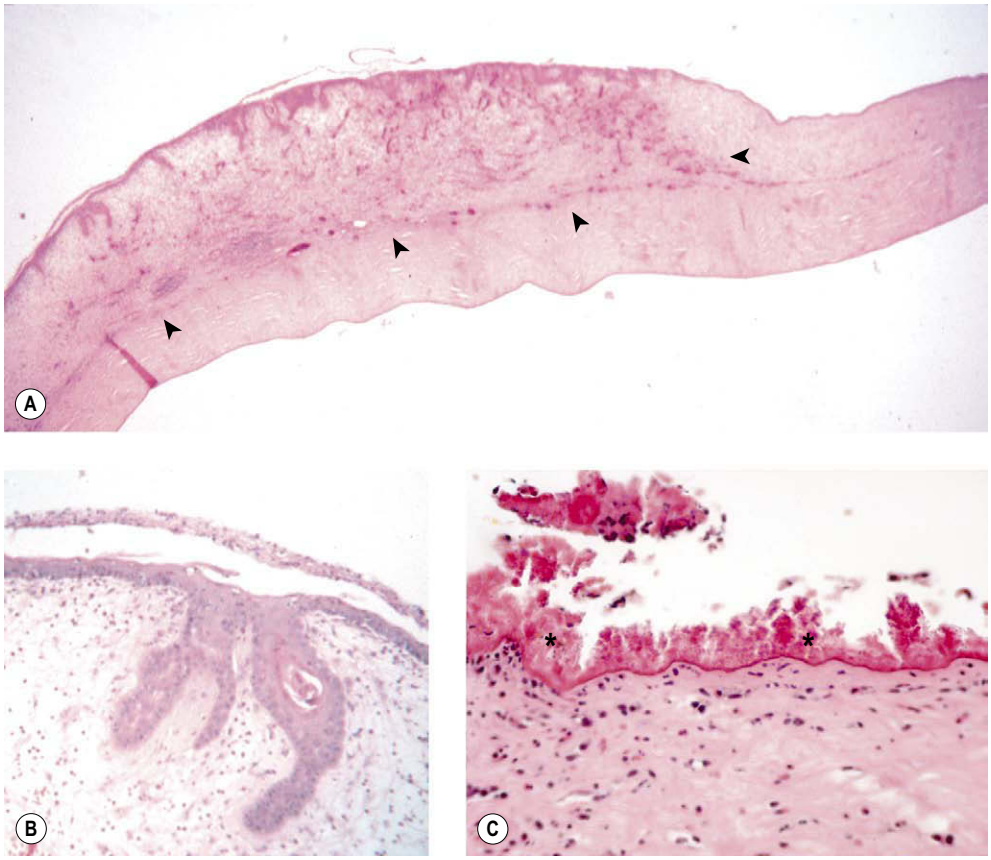


Figure 8.16 Feline eosinophilic keratitis, pathology. (A) Low magnification photomicrograph of a feline cornea showing the features of eosinophilic keratitis. There is abrupt effacement of anterior lamellar stroma by heavily vascularized, loose edematous connective tissue and an inflammatory cell infiltrate (arrows). (B) Higher magnification photomicrograph showing the surface epithelium with deep epithelial pegs extending into the loose stroma. (C) In this photomicrograph, an ulcerated surface is carpeted by hypereosinophilic protein material (*), a rare feature of feline eosinophilic keratitis.

  - This might be of stromal collagen origin or it might result from the degranulation of eosinophils
- Eosinophils and other inflammatory cells are seldom seen in samples submitted for pathology
  - This may be because the cases with abundant eosinophils are readily diagnosed based on clinical appearance and cytologic findings.

FELINE CORNEAL SEQUESTRUM (FELINE CORNEAL NECROSIS, CORNEA NIGRUM) (Figs 8.18, 8.19)

This condition is a commonly recognized clinical entity in cats. There are 111 feline cases documented in the COPLOW collection

Key features of corneal sequestrum include:

- Superficial ulceration characterized by a lack of epithelial attachment
  - Clinically, some cases fail to retain fluorescein dye suggesting that ulceration may not always be a feature of the disease. However, this may also reflect a failure of hydrophilic fluorescein dye to stain the relatively desiccated, hydrophobic sequestrum that is exposed
  - In some cases, there is a history of chronic, superficial corneal erosion or ulceration preceding sequestrum formation
- Stromal pigmentation
  - Brown pigmentation of the affected stroma is an early feature of the disease
  - In some cases, stromal discoloration is evident under an intact epithelium
  - The extent of pigmentation can range from barely detectable amber discoloration to dense, black opacity when observed clinically
  - The precise nature of the dark pigment remains unknown. Different laboratory analyses of keratectomy specimens both support and refute the presence of iron or melanin within the diseased tissue
- Morphologic features of feline corneal sequestrum include:
  - A localized superficial stromal defect characterized by superficial ulceration and brown to black discoloration of the diseased stroma
  - The lesion typically involves just the anterior stroma, although in rare instances the sequestrum involves the full thickness of the cornea
  - In addition to being discolored, the diseased stroma is devoid of keratocytes. The lamellar quality of the stroma is maintained but the normally distinct collagen lamellae appear to have blended together
  - Neither blood vessels nor inflammatory cells enter the sequestered stroma, and its collagen appears to resist enzymatic degradation
  - Opportunistic bacterial or fungal organisms are frequently seen, on or within the sequestered stromal tissue
  - Varying degrees of inflammatory cell infiltration, blood vessel in-growth, collagen degradation, edema and granulation tissue formation occurs at the periphery and deep margins of the lesion
  - Left untreated, the corneal epithelium will eventually undermine the sequestrum, causing the sequestrum to

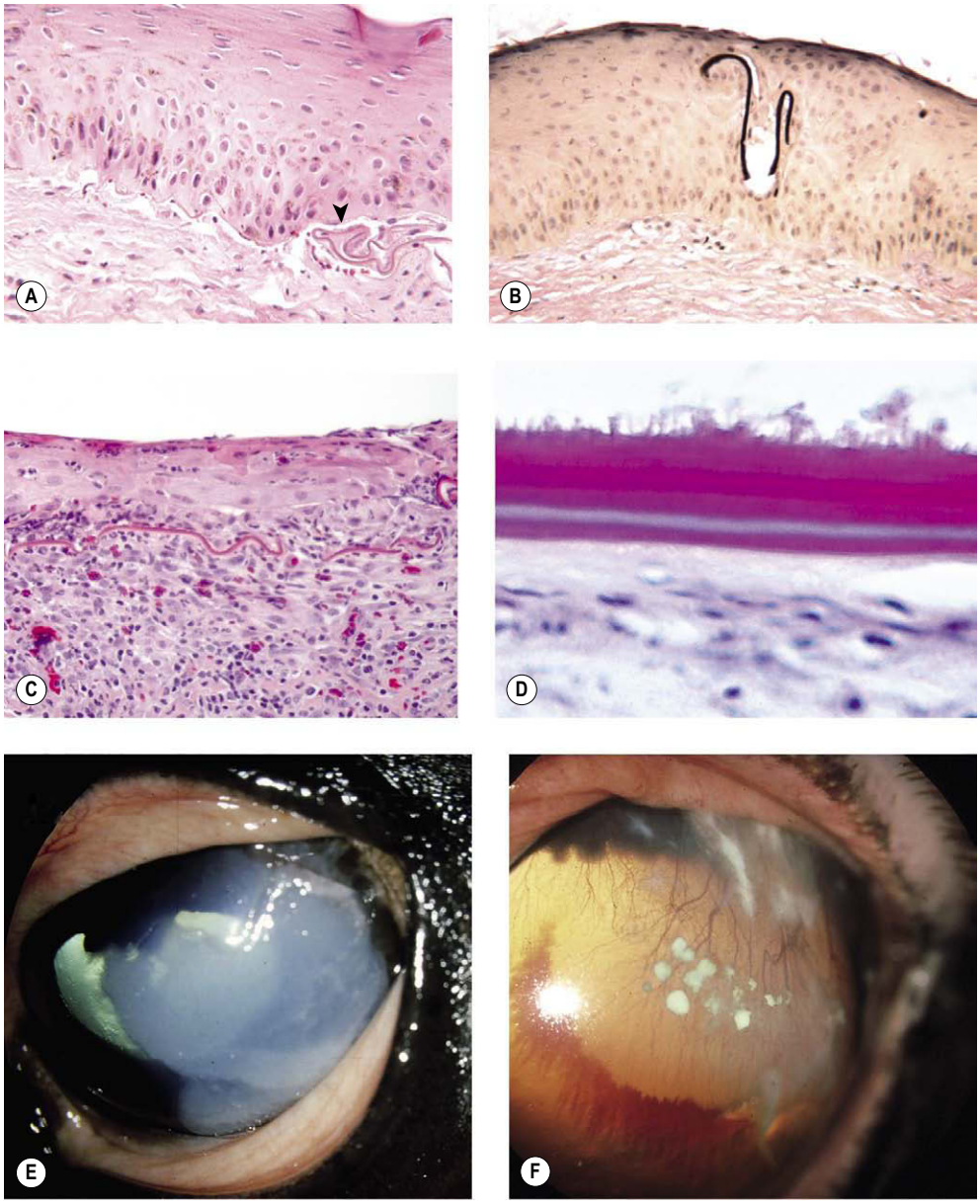


Figure 8.17 Equine superficial sequestrum/eosinophilic keratitis. (A) Photomicrograph of the epithelium from a horse with equine eosinophilic keratitis or superficial sequestrum. The thin membranous sequestered protein material is wrinkled at the base of the epithelium (arrow). (B) A fragment of sequestered membrane (black) is entrapped by the epithelium that has reformed around it (Verhoeff's elastic stain). (C) Photomicrograph showing a poorly attached epithelium, a wrinkled remnant of sequestered membrane and an eosinophilic infiltrate, an infrequent finding in a pathology specimen. (D) Photomicrograph showing a thick and doubled sequestrum membrane on the surface of an ulcerative lesion. (E) Thoroughbred, adult: the large white gritty superficial deposit was also fluorescein-positive. (F) American Quarter Horse, 11 years old: superficial corneal vessels and multiple white precipitates are present. Conjunctival cytology demonstrates many eosinophils. (Reproduced with permission from Hakanson N E, Dubielzig R R 1994 Chronic superficial corneal erosions with anterior stromal sequestration in three horses. Vet Comp Ophthalmol 4:179–183.)

slough, with subsequent spontaneous healing. However, this is often a very protracted process that may take weeks or months. Lesions that extend very deeply into the corneal stroma are unable to resolve spontaneously in this way

- The pathogenesis of corneal sequestration is poorly understood
  - There is a breed predisposition for the Persian cat, in which the disease is more likely to involve both eyes
  - In some cases, there may be a history of prior corneal insult, injury and/or ulceration that appears to incite the process of sequestrum formation
  - There is strong, but equivocal evidence to support a role for FHV-1 in the pathogenesis of corneal sequestration in non-predisposed breeds. Topical corticosteroid therapy may also predispose to corneal stromal sequestration in cats.

CORNEAL SEQUESTRATION IN OTHER SPECIES (Fig. 8.20)

Although seldom mentioned in the published literature, morphologic features of corneal sequestrum are seen occasionally in eyes or keratectomy specimens from other species, including dogs and horses. There are 42 cases of corneal sequestrum in dogs recorded in the COPLOW collection.

- As mentioned below, recurrent erosion syndrome shares several features with sequestration
- Equine eosinophilic keratitis and at least a subset of equine chronic superficial erosions have a superficial acellular protein membrane reminiscent of that seen in feline sequestrum
- Brown pigmentation of the sequestered stromal tissue is seldom seen in species other than the cat

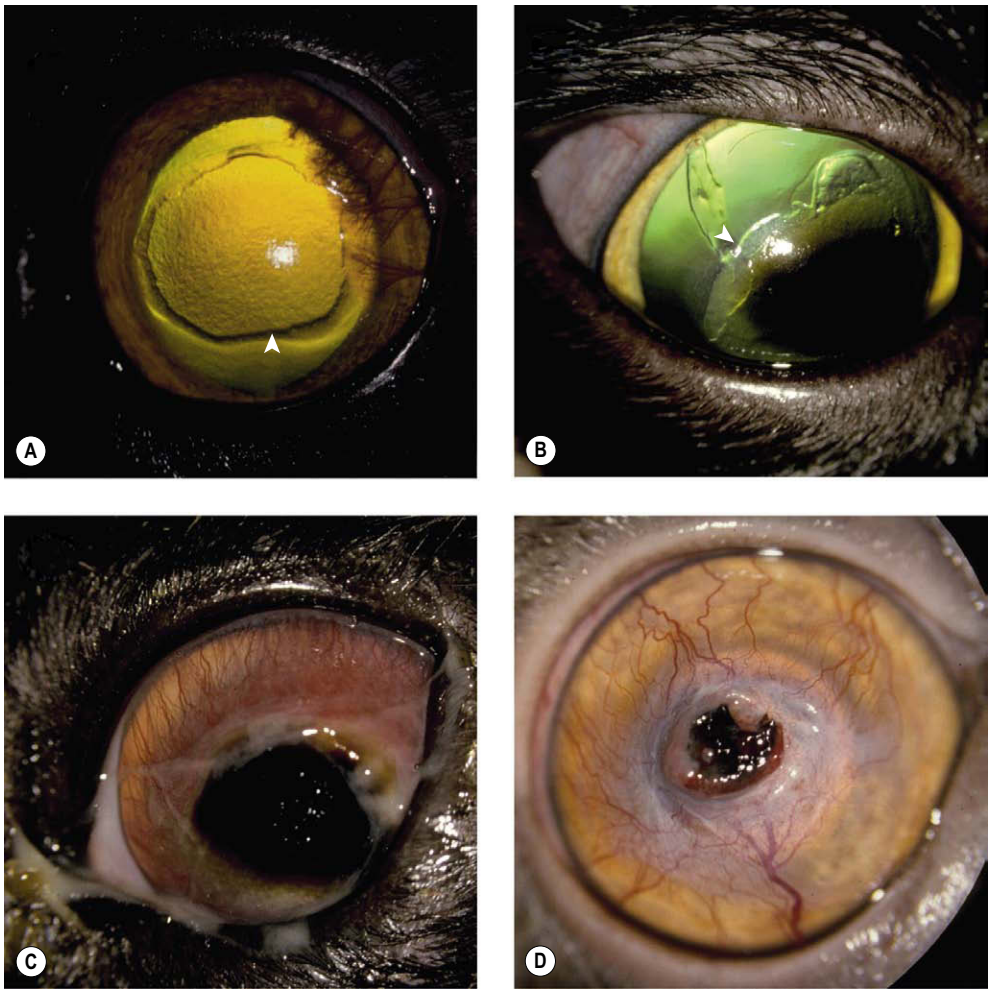


Figure 8.18 Feline corneal sequestrum, clinical. (A) Persian, 10 months old: the axial corneal stroma illustrates bronzing. The dark elliptical ring (arrow) represents the extent of the superficial ulcer. (B) Bombay, 2 years old: the cornea is ulcerated over the dense sequestrum. The loose epithelium can be seen at the margin of the ulcer (arrow). (C) DSH, 5 years old: a zone of necrosis and corneal vessels surrounds the dense superficial sequestrum. (D) DSH, 7 years old: the axial sequestrum is elevated and is about to be extruded from the corneal surface.

- Opportunistic microorganisms are often found within the sequestrum, just as in cats
- Animals with a history of sudden corneal exposure or acute keratoconjunctivitis sicca (KCS), and subsequent profound desiccation of the ocular surface, can develop necrosis and sequestration of their anterior corneal stroma
  - One published report documents absolute KCS associated with development of an equine corneal sequestrum that was clinically and histologically indistinguishable from the feline disease.

RECURRENT EROSION SYNDROME (INDOLENT ULCER, BOXER ULCER, SPONTANEOUS CHRONIC CORNEAL EPITHELIAL DEFECTS) (Figs 8.21, 8.22)

This condition is very commonly encountered in dogs, but similar clinical presentation and pathology are seen in other species, including cats, horses and rabbits

- A strong breed predisposition has been documented for Boxer dogs, although all breeds can be affected
- In globes submitted for pathological assessment, this condition is very often found as an incidental finding and not the focus of clinical attention
- The characteristic clinical features of recurrent erosion include:
  - Superficial ulcer/erosion that lacks stromal involvement
  - A flap or lip of non-adherent epithelium surrounds the margins of the defect
  - The ulcer resists healing and may persist for many weeks or often months if not treated appropriately
  - Although the individual response to the presence of these lesions is highly variable, the degree of associated discomfort, extent of neovascularization and inflammatory response may be minimal, despite their chronicity
  - Ulceration may recur in either eye
- Pathologic features of recurrent erosion include
  - The adjacent, non-adherent epithelium exhibits dysmaturation and undergoes a morphologic change such that both its superficial and basal surfaces keratinize
  - The basal lamina is essentially absent in the affected area, but fibronectin coats the exposed stroma
  - There is a relatively thin, hyalinized, acellular zone in the superficial stroma and any inflammatory cellular infiltrate, fibroplasia or vascularization occurs deep to this acellular

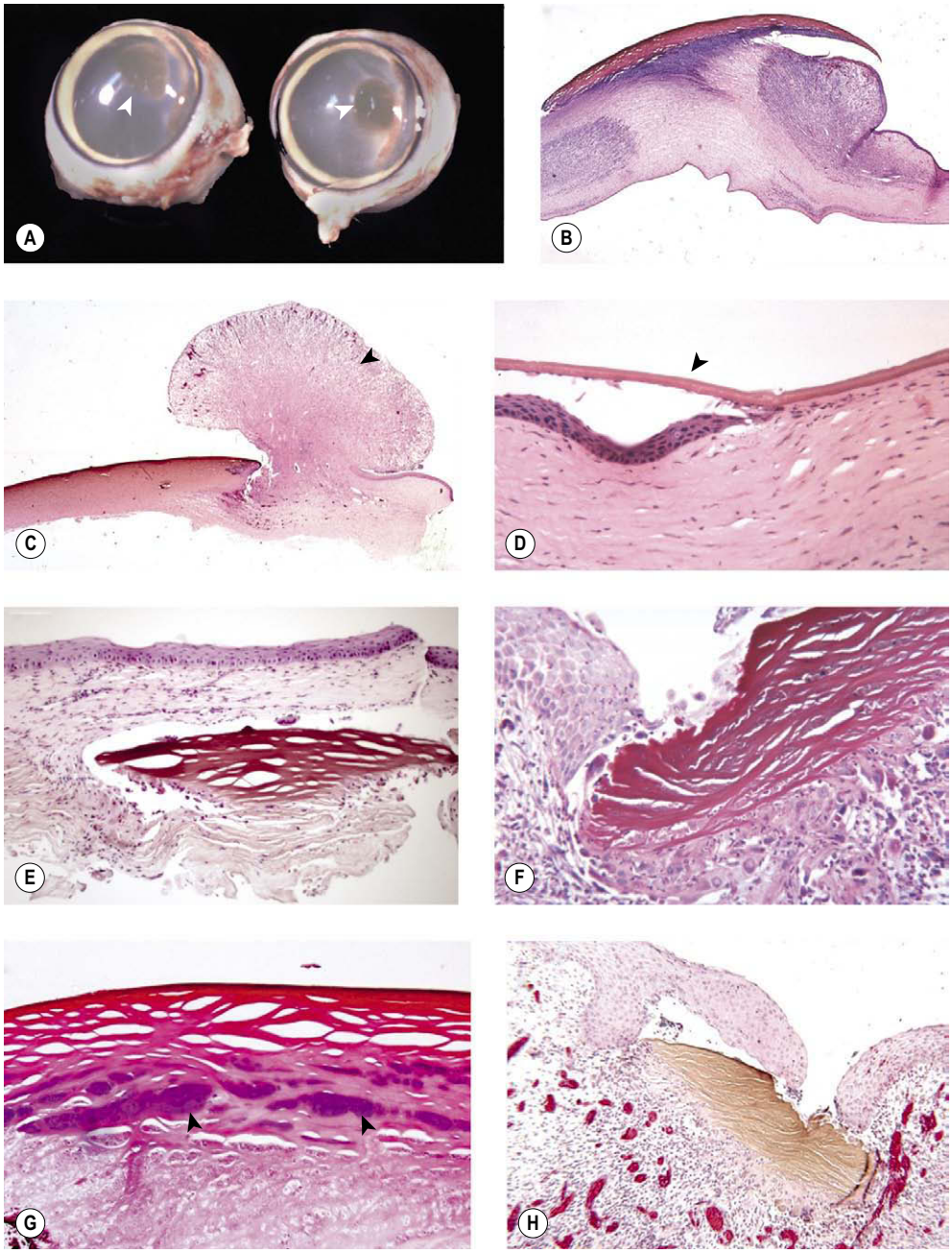


Figure 8.19 Feline corneal sequestrum, pathology. (A) Gross photograph of left and right feline globes showing pigmented sequestrum (arrows). (B) Low magnification photomicrograph of feline cornea showing a superficial pigmented sequestrum (brown) in the process of sloughing off the surface of the inflamed cornea. (C) Low magnification photomicrograph of a keratectomy specimen from an affected cat showing a brownish superficial sequestrum and, at the margin, there is an exophytic overgrowth of granulation tissue (arrow). (D) Photomicrograph showing the corneal epithelium healing by sliding underneath the more superficial sequestrum (arrow). (E) A fragment of sequestrum stroma is embedded within a healed corneal defect. (F) Higher magnification photomicrograph showing the healing response at the margins of sequestered stroma. There is a foreign body-like macrophage response, and inflammatory cells do not migrate into the sequestrum itself. (G) Photomicrograph of feline sequestrum colonized by opportunistic bacterial colonies (arrows). (H) A fragment of sequestrum is surrounded by granulation tissue, however the sequestrum itself is free of any cellular infiltrate of protease degradation.

zone. The acellular layer might be as thin as 20 µm and as thick as 100 µm

- There are many similarities between recurrent erosion and corneal sequestration:
  - The lack of epithelial attachment at the margins of the lesion
  - The acellular superficial stroma which resists degradation and infiltration
  - Occasionally the acellular superficial stroma will mineralize and behave like a sequestrum
  - Development of corneal sequestra has been documented at the site of non-healing erosions in cats
- No single cause for this condition is recognized
  - Although the initiating cause may be minor, superficial trauma, the syndrome's characteristic morphologic features are not merely the result of chronic injury to, or a chronic defect in, the corneal surface
  - Absence of basement membrane and abnormalities in the anterior stroma appear to play a key role in the lack of epithelial adhesion and delayed healing of these lesions. Surgical procedures that disrupt the abnormal basement membrane and anterior stroma, such as epithelial debridement, keratectomy, anterior stromal puncture and grid keratotomy are generally required to promote healing. However, repeated surgical debridement does not lead to the formation of a condition similar to chronic erosion
  - Altered patterns of corneal innervation and neuropeptides have been documented in dogs with recurrent erosions

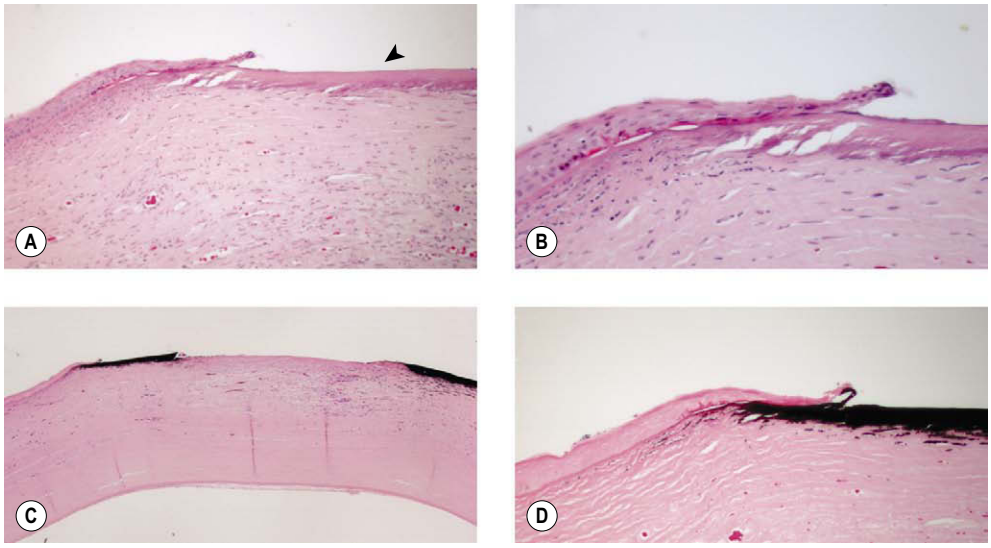


Figure 8.20 Canine corneal sequestrum. (A) Photomicrograph showing canine superficial sequestrum (arrow) with ulceration and failure of the epithelium to attach to the corneal surface. (B) Higher magnification of (A). (C,D) Mineralized canine corneal sequestrum (von Kossa stain).

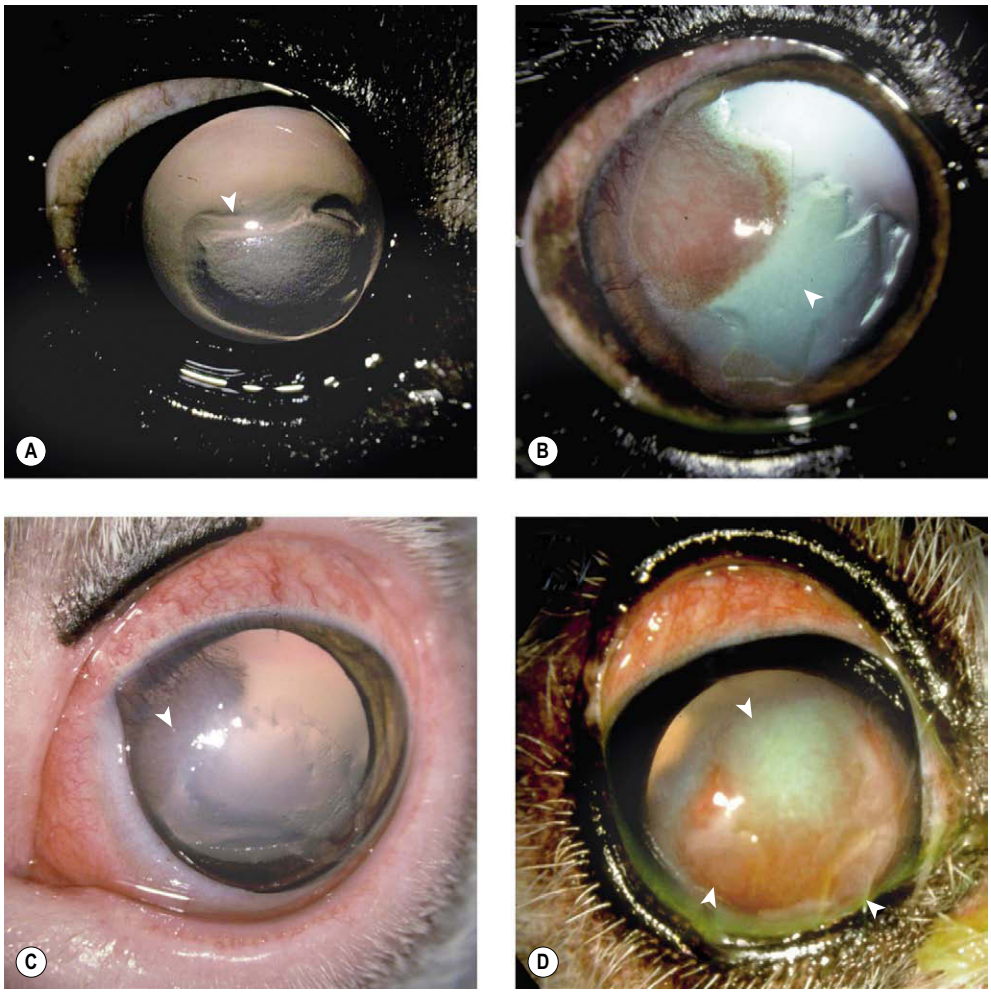


Figure 8.21 Recurrent erosion, clinical. (A) Labrador Retriever cross, 5 years old: the arrow indicates the redundant non-attached epithelium that surrounds the area of superficial ulceration. (B) Boxer, 9 years old: the stroma in the area of ulceration is edematous (arrow). (C) Boxer, 8 years old: after a 3-month history of ulceration, blood vessels are invading the cornea (arrow). (D) West Highland White Terrier, 11 years old: positive fluorescein stain, redundant epithelium and vessels outline this ulcer (arrows).

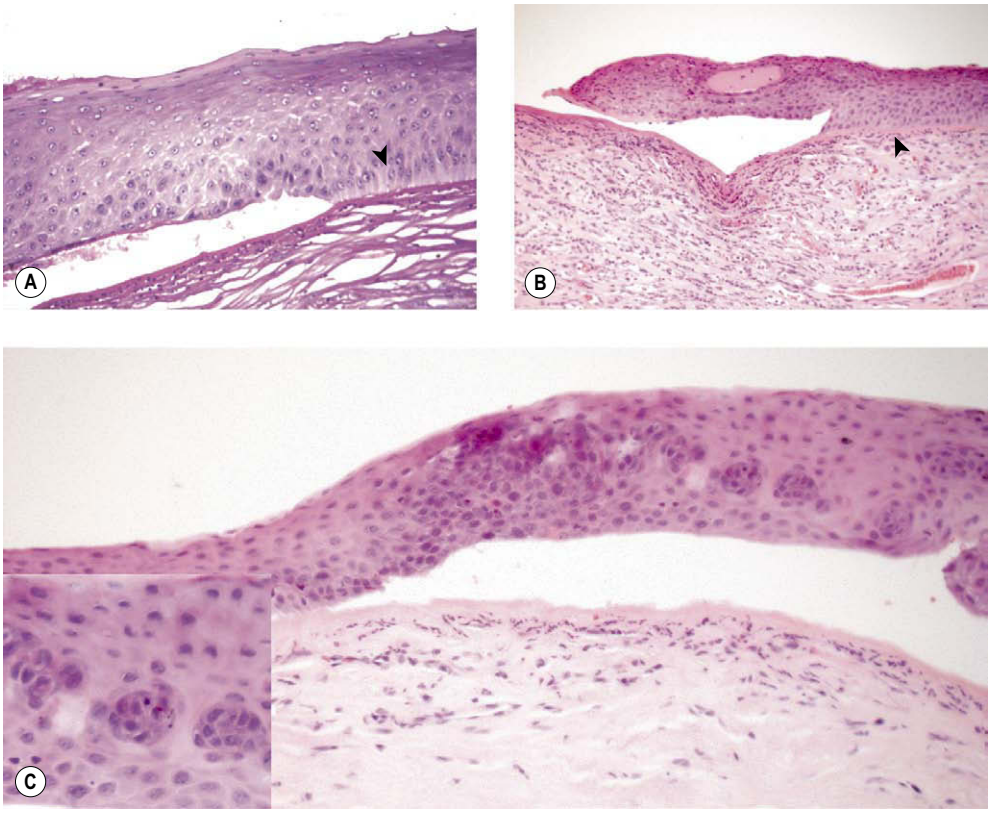


Figure 8.22 Recurrent erosion, pathology. (A) Photomicrograph showing the point of epithelial non-attachment in recurrent erosion. The unattached epithelial flap has lost some of the organizing features of the attached epithelium, particularly the columnar nature of the basal cells (arrow). (B) Photomicrograph similar to (A) showing an inflamed superficial stroma and a prominent superficial acellular layer (arrow). (C) Higher magnification photomicrograph showing a lack of polarity in the unattached epithelium and localized epithelial whorls (inset).

- Altered expression of factors that promote epithelial migration and adhesion have been documented
- Some affected dogs demonstrate increased proteolytic activity in their tear fluid and respond to protease inhibitor therapy
- Severe stromal edema leading to lifting of the epithelium associated with subepithelial bullae can lead to several morphologic features similar to chronic erosion

- Florida keratopathy (Florida spots), focal corneal stromal opacification (Fig. 8.23)
  - This condition is characterized by one or more localized round foci of corneal stromal opacification in dogs or cats with no symptoms of pain or inflammation
  - Five globes with this condition have been examined at the COPLOW laboratory and, in contrast to a previous report, no evidence of abnormal morphology, or of associated pathologic organisms, has been found in any of our specimens by histopathology.

FUNGAL KERATITIS, EQUINE AND OTHER SPECIES (Figs 8.24, 8.25)

There are 75 cases of fungal keratitis in horses in the COPLOW collection, which represents 10% of all equine submissions. There are 18 cases in dogs and two cases in cats.

Fungal keratitis is most frequently encountered in horses, particularly in certain geographic locations such as the South-Eastern United States. Fungal keratitis is relatively rare in most other domestic species.

The route of infection is not well documented, but it is widely believed that pre-existing disruption of the corneal epithelial barrier, or traumatic implantation of these opportunistic pathogens, is necessary to establish fungal keratitis.

However, epithelial microerosions have been identified in horses at an early stage in the development of mycotic keratitis, which may indicate that complete removal of the epithelial barrier may not be necessary to fungal colonization of the cornea.

- *Aspergillus* sp. are most commonly implicated but *Fusarium* sp. and others are also found.

Infection can be superficial stromal, deep stromal (at the level of Descemet's membrane), or both superficial and deep. The clinical presentation of fungal keratitis is therefore highly variable:

- Ulcerative keratitis with variable stromal involvement. Often a plaque of white, yellow or brown material is present on the surface of the lesion
- Keratomalacia may occur, and may be a direct result of proteases liberated by fungal organisms (see below)
- Stromal abscess formation may occur deep in the cornea, and in some cases the abscess may be seen to bulge posteriorly into the anterior chamber
- Morphologic characteristics of fungal keratitis include:
  - Suppurative inflammation or, more rarely, pyogranulomatous inflammation
  - Presence of fungal hyphae within Descemet's membrane
  - Multiple breaks in Descemet's membrane are often present near the site of fungal colonization
  - Silver stains for fungi are often needed to help visualize the organisms
  - It the original section does not sample the site with the organisms, it might be necessary to step-section deeply into the block in order to find the fungi

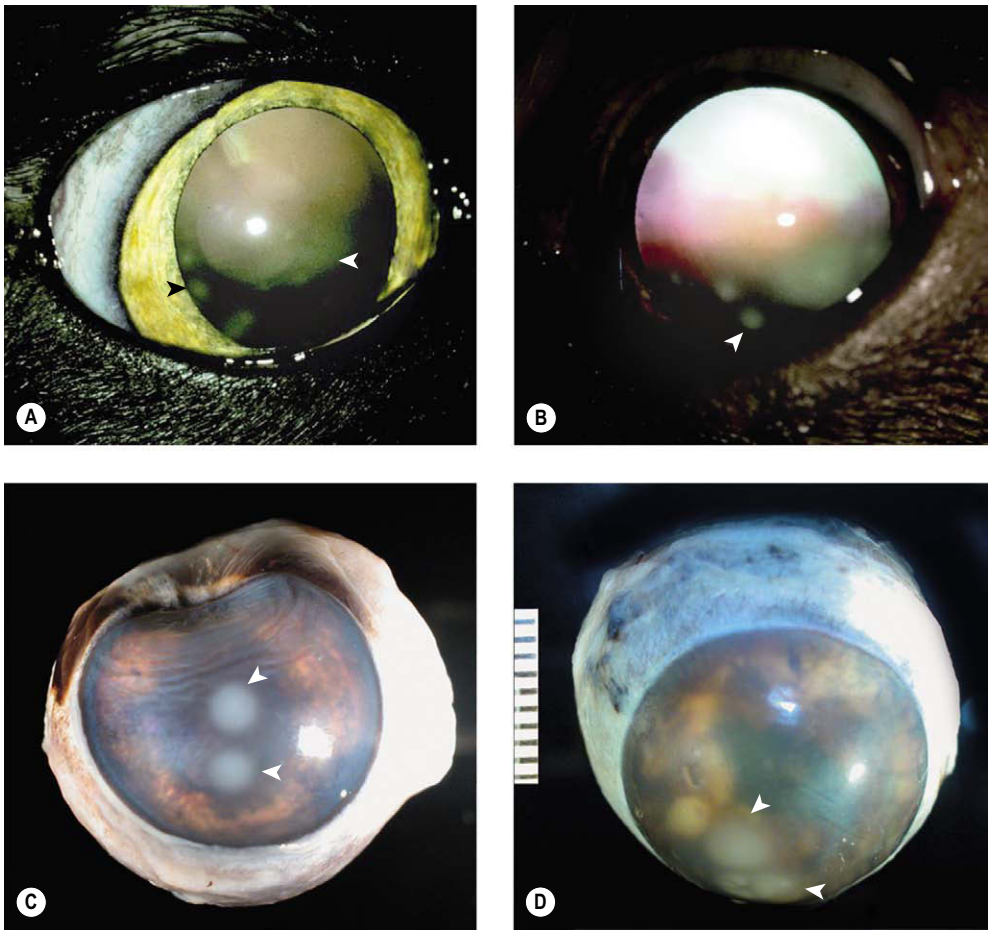


Figure 8.23 Florida spots. (A) DSH, 10 years old: this cat from Venezuela was presented with bilateral, multiple focal opacities in the superficial cornea best seen by retroillumination (arrows). (B) Mixed canine, 6 years old: this dog was a rescue dog from Florida. The bilateral opacities were located in the deep epithelial and superficial stroma (arrow). (C,D) Gross photographs showing the corneas of two cat eyes with foci of corneal opacity (arrows) diagnosed as Florida Spots clinically. No changes were recognized on histopathology.

- Tissues containing fungal organisms often lack a significant neovascular response, and the production of anti-angiogenic factors by pathogenic fungi has been proposed
- Definitive identification of fungal organisms from histopathology or cytology is difficult, therefore isolation of the organism (which is time consuming) is often required for its identification. Recently, molecular genetic techniques have been used in the diagnosis of fungal keratitis.

KERATOMALACIA, COLLAGENOLYTIC KERATITIS, MELTING CORNEAL ULCER (Figs 8.26, 8.27)

Keratomalacia is a devastating disease process which occurs in all species.

- Horses are commonly presented with keratomalacia, secondary to microbial keratitis
- This is also seen in dogs but more rarely
  - Brachycephalic dog breeds that typically have prominent globes and lagophthalmos (e.g. Shih Tzu, Pekingese, Pug) appear predisposed to severe keratomalacia.

Increased proteolytic activity occurs to some degree in most inflammatory conditions of the cornea, and in normal wound healing. Keratomalacia occurs when the lysis of stromal collagen proceeds rapidly and unchecked, overwhelming normal tissue mechanisms of protease inhibition and resulting in liquefaction of the corneal stroma.

Topical corticosteroids potentiate the activity of proteases and predispose to microbial keratitis.

Serine proteases and matrix metalloproteases (MMPs) are released by certain micro-organisms, inflammatory cells and by native cells (including epithelial cells and keratocytes). A number of different pathogenic mechanisms may therefore be responsible for triggering keratomalacia, including:

- Microbial keratitis: Any form of microbial infection can incite an inflammatory response and can lead to liberation of endogenous proteases
- Bacterial keratitis: Bacteria are seen in histopathology only in the most early stages of disease and, in those cases, bacteria can be numerous. The lack of bacterial organisms in pathology submissions with keratomalacia may be due to prior therapy with antibiotics
  - Certain bacteria, most notably *Pseudomonas aeruginosa*, produce exogenous MMPs and have a well-defined association with keratomalacia
  - Mycotic keratitis (see above)
  - Certain fungal organisms, e.g. *Aspergillus* and *Fusarium* spp., produce extracellular serine proteases
  - Viral keratitis
- Chemical injury
  - Particularly alkali burns
- Trauma or acute, severe corneal desiccation

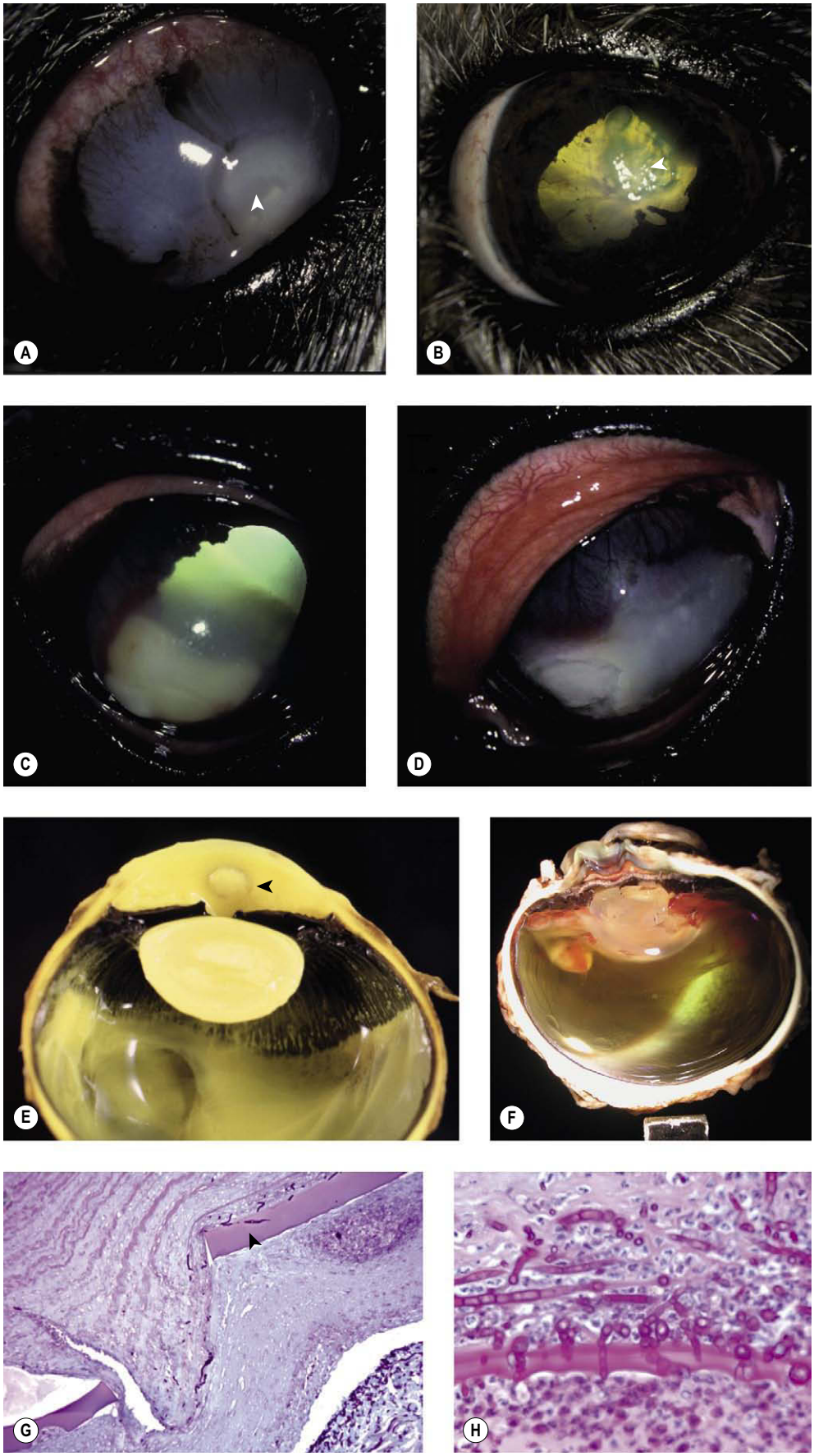


Figure 8.24 Mycotic keratitis. (A) Mixed Breed, 13 years old: *Aspergillus flavus* was cultured from the area of keratomalacia (arrow). (B) Shih Tzu, 10 years old: *Candida parapsilosis* was cultured from the area of the ulceration at the arrow. (C) Thoroughbred, yearling: *Mucor* sp. was cultured from the ulcerated cornea and from the stromal abscess. (D) Thoroughbred, 6 years old: *Fusarium* sp. was cultured from the large area of malacia. (E) Gross photograph of an equine globe fixed with Bouin's fixative. A posterior stromal abscess is seen bulging into the anterior chamber (arrow). (F) Gross photograph of an equine globe after conjunctival graft showing deep stromal suppurative inflammation and narrowing of the exudate-rich anterior chamber. (G) Photomicrograph showing *Aspergillus* fungal hyphae in ruptured Descemet's membrane (arrow) in a horse (GMS stain). (H) Photomicrograph showing *Mucor* fungal hyphae in the Descemet's membrane from a diabetic dog (PAS stain).

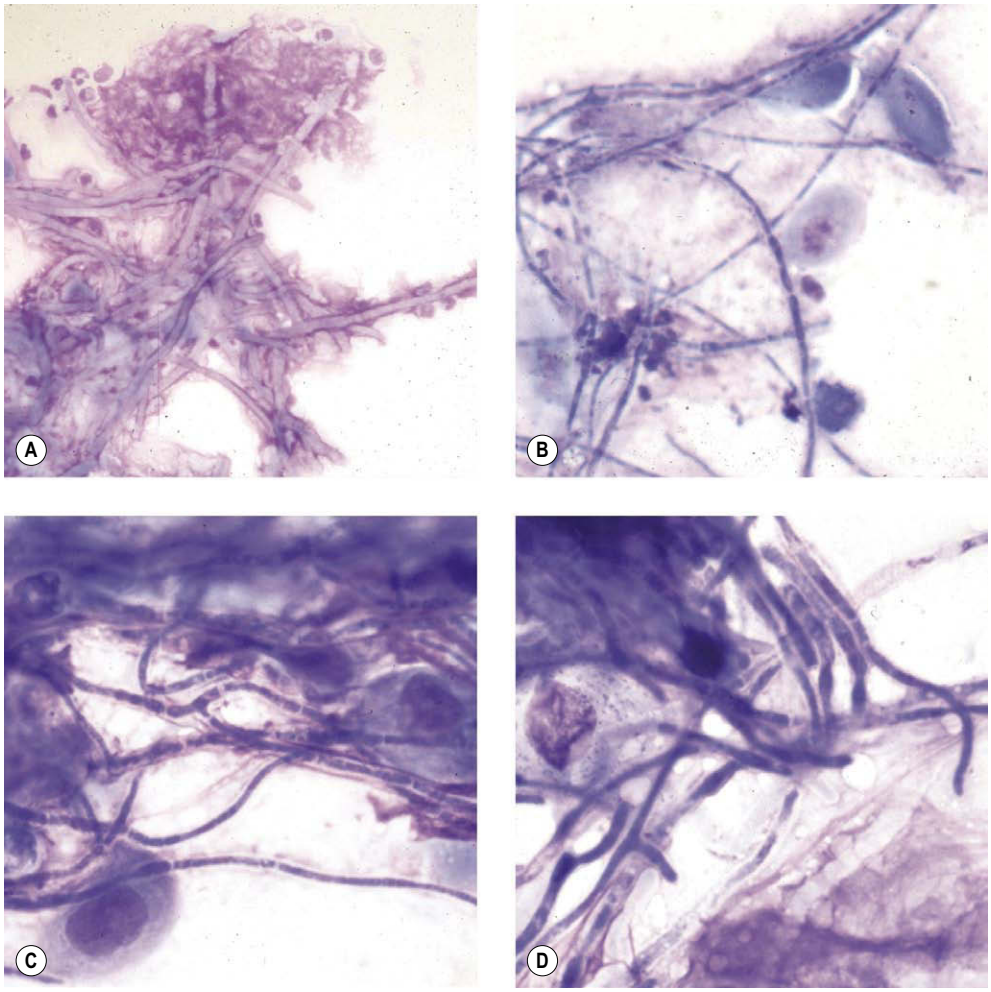


Figure 8.25 Corneal mycotic cytology (based on morphology). (A) *Mucor* sp. (B) *Aspergillus* sp. (C) *Alternaria* sp. (D) *Acremonium* sp.

- In many cases, the initiating cause cannot be determined histopathologically

Morphologic features of keratomalacia include:

- Abrupt qualitative change in the corneal stromal morphology
  - The normal lamellar stroma is markedly altered
    - Loss of lamellar architecture
    - Loss of birefringence
    - Collapse of the tissue owing to a loss of structural support because of the liquid nature of the affected tissue
  - Usually collagenolytic lesions are rich in neutrophils, many of which are degenerate
- Descemetocele formation may be followed by corneal perforation and iris prolapse if keratomalacia is not controlled.

The prognosis for maintenance of vision in globes with perforations following keratomalacia is poorer than that for globes with traumatic, penetrating injury because of the increased likelihood of intraocular infection.

Comparative Comments

The discussion included in this chapter regarding superficial chronic keratitis, recurrent erosion syndrome, collagenolytic keratitis, corneal lysis, and corneal perforation is generally consistent with what the ocular pathologist notes in human eyes with similar conditions.

Infectious ulcerative keratitis may occur in humans, as in other species, as a result of viral, bacterial, fungal, and protozoal infection.

- The most common viral pathogens affecting the human cornea are herpes simplex and herpes zoster
- Bacterial infections usually follow disruptions of the integrity of the surface epithelium
  - The most important predisposing condition is trauma, including trauma from contact lenses, as well as bullous keratopathy and connective tissue disorders
  - Syphilis may give rise to interstitial keratitis
  - Bacterial crystalline keratopathy is a condition that results from suppression of the inflammatory response due to steroids in which there is unchecked bacterial proliferation in the stroma
    - White crystalline stromal opacities are seen clinically, and on microscopic examination, clumps containing massive numbers of bacteria occur in the stroma
- Fungal infections may also follow corneal trauma, particularly when plant material is introduced into the cornea
  - In humans, mycotic keratitis is often seen in immunocompromised or debilitated patients and may be associated, as well, with the use of certain contact lens solutions
- In recent years, *Acanthamoeba* keratitis has become a growing problem in humans, associated with reusable contact lenses

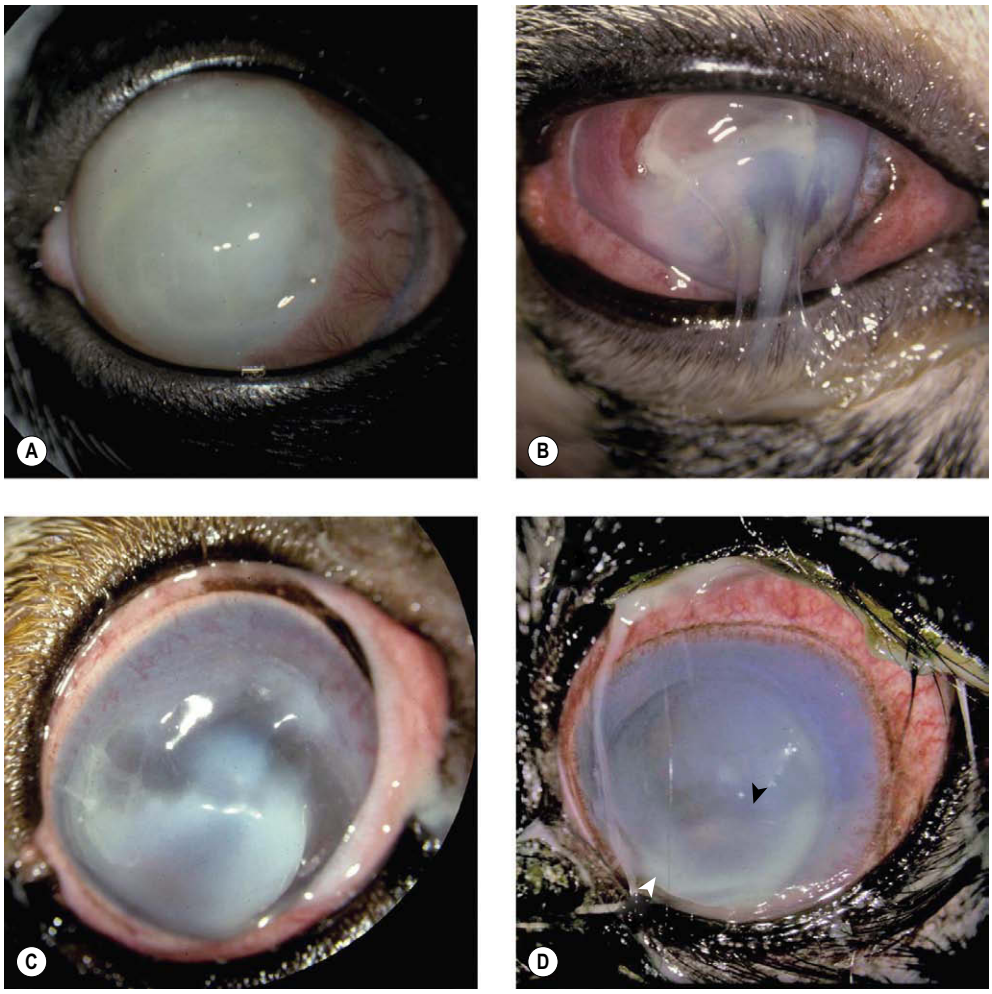


Figure 8.26 Keratomalacia (collagenolytic keratitis), clinical. (A) DSH, 8 years old: *Pseudomonas aeruginosa* was cultured from this severe case of keratomalacia. (B) DSH, 6 years old: *Mycoplasma felis* was cultured and identified from the axial cornea. (C) French Bulldog, 1.5 years old: *Capnocytophaga* sp. was cultured from the axial cornea. (D) Pekingese, 11 years old: the white arrow points to the site from which *Pseudomonas* sp. was cultured. The black arrow points to the hypopyon.

Comparative Comments (continued)

inappropriately cleaned, and with increasing contamination in tap water and swimming pools
- The *Acanthamoeba* exists in two forms, trophozoite and cyst
- It gives rise to a clinical picture similar to herpes keratitis but is resistant to treatment.

CORNEAL PERFORATION (see also Ch. 5)

COPLOW receives many enucleated globes from animals with perforating corneal lesions.

- Some are submitted in the immediate aftermath of perforation, when owners elect not to pursue further treatment on the grounds of cost, when given a poor prognosis for vision in the affected eye
- Some are submitted when severe endophthalmitis sets in
- Some are submitted when intractable glaucoma sets in.

It can be hard to recognize prior corneal perforation, particularly in globes that have extensive corneal scar tissue formation, but the following features are helpful (Fig. 8.28):

- Rupture of Descemet's membrane
- Full thickness corneal scar replacing the lamellar stroma
- Entrapment of pigmented uveal tissue within the stromal scar
- Anterior synechia, at the perforation site, or more extensively.

CORNEAL LYSIS, PERFORATION, AND IRIS PROLAPSE WITH EPITHELIALIZATION IN YOUNG CATS (Fig. 8.29)

There are four cases of young cats, ranging in age from 4 months to 7 years, in the COPLOW collection with subtotal lysis of the cornea followed by epithelialization of the prolapsed iris tissue.

- Both history and morphology suggest that affected cats experienced a catastrophic, destructive ocular event as a neonate, perhaps prior to eyelid opening (i.e. *ophthalmia neonatorum*)
- In all cases, the affected globe was small, wrinkled and aphakic, in the absence of significant inflammation or osseous metaplasia. Affected cats demonstrated minimal signs of discomfort
- While there is no specific evidence implicating *FHV-1* infection as the cause of this syndrome, this would seem to represent a likely cause that warrants consideration.

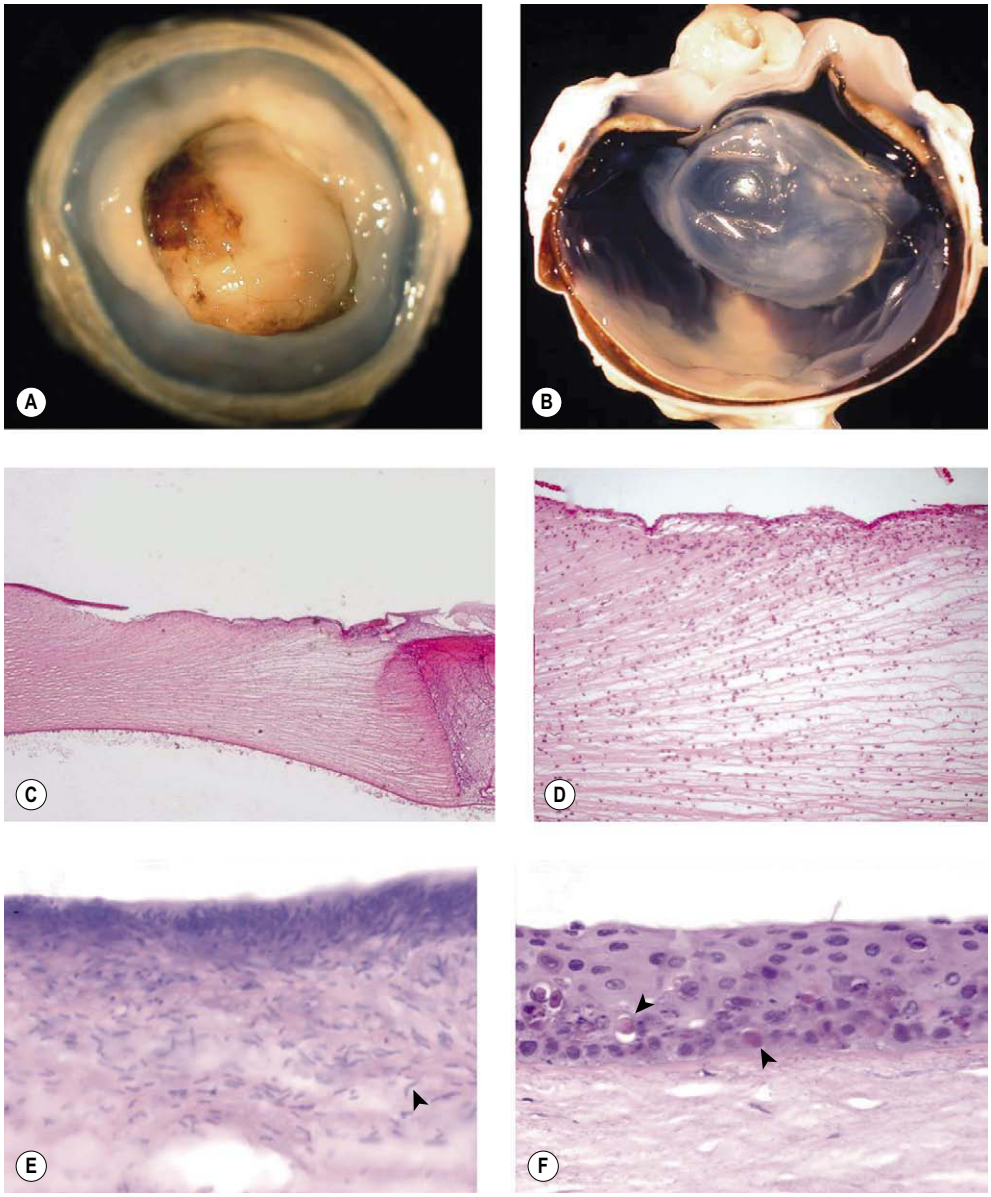


Figure 8.27 Keratomalacia (collagenolytic keratitis), pathology. (A,B) Gross photographs of a feline globe showing an elevated soft central corneal stroma typical of collagenolysis. (C,D) Photomicrographs of a canine cornea showing early collagenolysis. There is a suppurative infiltrate, and the corneal lamellar stroma is being degraded and liquefied. (E,F) Photomicrographs of a canine cornea from an eye removed only hours after a traumatic event. Collagenolysis is not yet apparent. Ulceration and extensive stromal *Pseudomonas* bacterial organisms (arrow) are present in (E). Epithelial degradation and necrosis (arrows) appear in (F).

EARLY LIFE CORNEAL PERFORATION, EARLY LIFE TRAUMA SYNDROME, AND ANTERIOR CHAMBER COLLAPSE SYNDROME (Fig. 8.30)

There are 59 cases in the COPLOW collection; including 27 cases in cats and 30 cases in dogs.

- Affected globes are from young animals, representing a range of species
  - The age at enucleation varies widely, but is usually less than 1 year
- Generally, eyes are enucleated because they have glaucoma and marked buphthalmos
  - A small proportion have phthisis bulbi and not buphthalmos
- They may or may not have a reported history of antecedent ocular disease, or ocular trauma early in life. It is important, but not easy, to distinguish this acquired syndrome from congenital ocular malformation, i.e. syndromes associated with anterior segment dysgenesis
- Morphologic features leading to a diagnosis of early life corneal perforation include:
  - Iris tissue broadly adherent to the posterior cornea
  - Full thickness corneal scar tissue
  - Pigmented uveal tissue entrapped in the fibrotic remnants of the corneal stroma
  - Descemet's membrane remains thin and is focally absent in segments of the diseased cornea
    - Descemet's membrane is often doubled, absent, or markedly attenuated
  - Often, there is minimal uveal inflammation
  - Lens abnormalities may include:
    - Microphakia or aphakia
    - Displaced lens remnants
    - Remnants of empty wrinkled lens capsule may be found
      - Often, but not always, at or within the corneal scar.

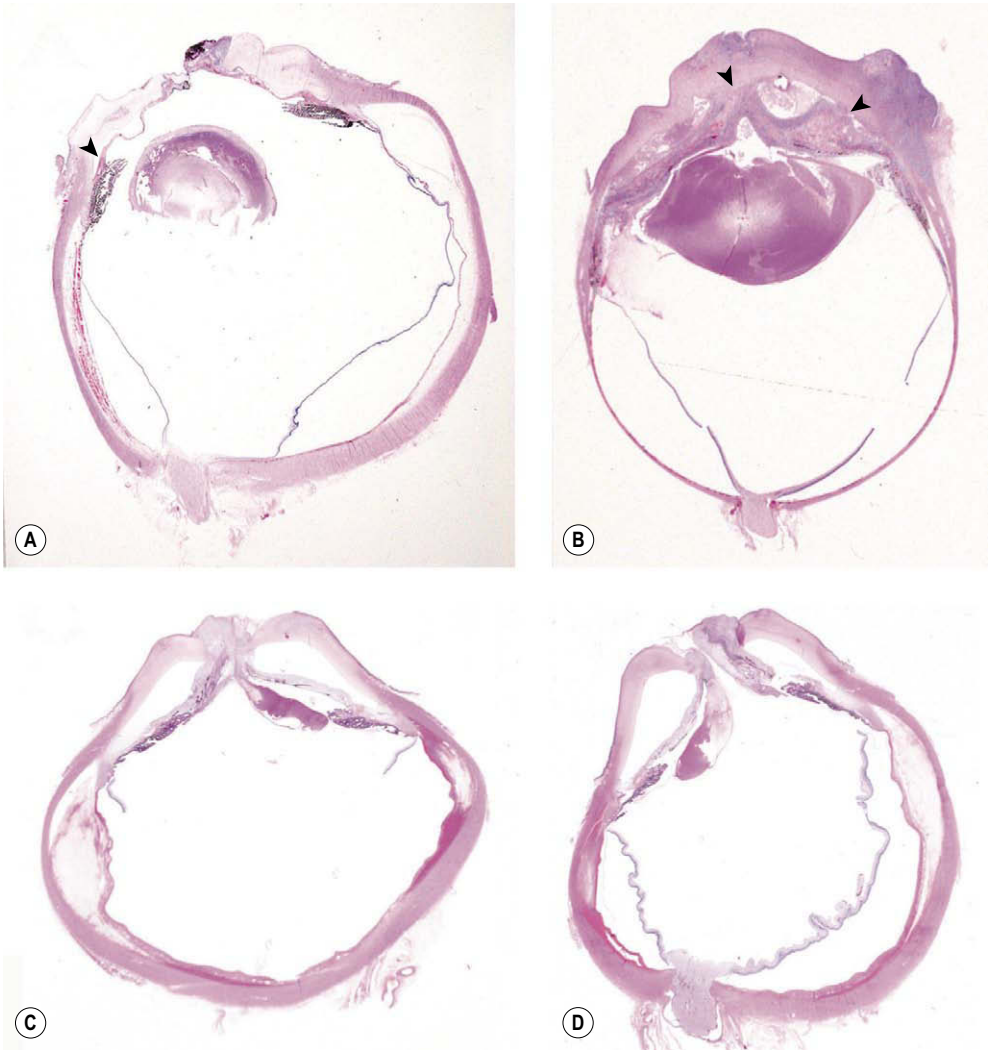


Figure 8.28 Corneal perforation and healing. (A–D) Four subgross photomicrographs showing globes that have healed and sealed over after corneal perforation and iris prolapse (A, equine; B, canine; C, bovine and D, equine). (A,B) have broad anterior synechia with narrowing of the anterior chamber (arrows).

CORNEAL EPITHELIAL INCLUSION CYST (see also Ch. 4)

- An uncommon, but important, differential consideration for corneal masses, such as dermoid, nodular granulomatous episclerokeratitis, corneal stromal abscess or corneal neoplasia
- These are predominantly acquired lesions and there is often a history of prior corneal disease such as corneal ulceration, or of surgical or non-surgical trauma, prior to cyst development
- Clinical appearance is of smooth, raised mass or masses. The cysts are associated with a variable degree of neovascularization of the adjacent stroma and range in color from white to pale yellow or pink
- There is seldom any associated discomfort
- These intra-stromal cysts consist of a non-keratinized squamous epithelial lining and lumen that is filled with a serous fluid of varying viscosity, color and cellularity.

INFLAMMATION DISRUPTING THE ENDOTHELIUM, ENDOTHELIITIS

Corneal edema may accompany anterior uveitis of any cause, examples include:

- Equine recurrent uveitis
  - Antigens common to both *Leptospira* spp. and the equine cornea have been implicated in the immunopathogenesis of recurrent uveitis in some horses
- Feline idiopathic lympho-plasmacytic uveitis
  - Localized endothelial cell inflammation can be associated with localized corneal edema.

Specific viral infections are strongly associated with inflammation of the corneal endothelium:

- Canine 'blue eye', Canine adenovirus type-1 (CAV-1), infectious canine hepatitis) (Fig. 8.31)
  - The descriptor 'blue eye' refers to the dense corneal edema which develops secondary to virus infection and

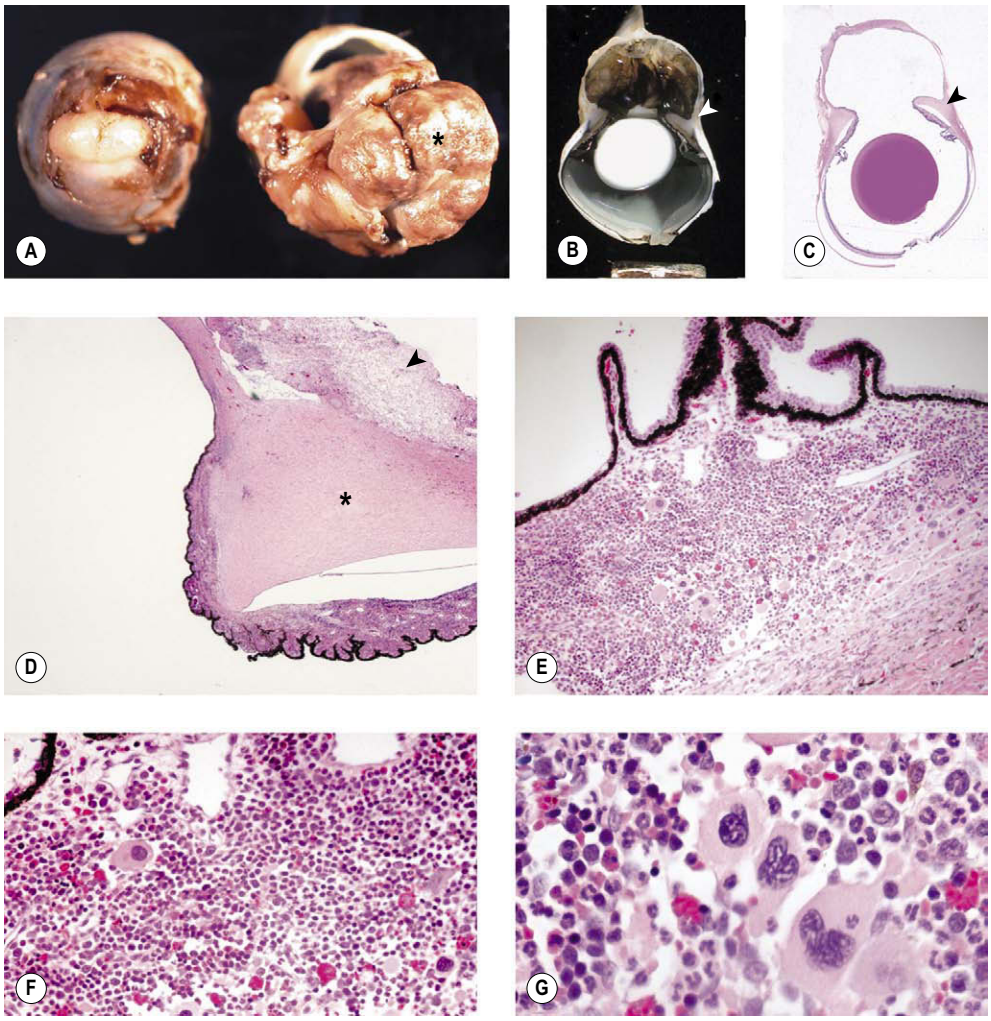


Figure 8.29 Feline early life corneal perforation. (A) Both globes from a young cat showing broad central corneal disruption and lysis in the neonatal period. The globe on the right has prolapse and subsequent epithelialization of uveal tissue (*). (B,C) Gross photograph and subgross photomicrograph showing a broad central corneal defect with iris prolapse and re-epithelialization. The central corneal degeneration was thought to have occurred in the neonatal period. Notice that the most peripheral corneal stroma is well preserved (arrows). (D) Photomicrograph showing the abrupt full-thickness disruption of the cornea with iris prolapse. The peripheral corneal stroma remains largely normal (*), while the conjunctival substantia propria covers the cornea (arrow). (E–G) Progressively higher magnification photomicrographs showing the cellular infiltrate in cat globes with broad corneal defects, iris prolapse and re-epithelialization. Much of the infiltrate is, in fact, extramedullary hematopoiesis.

subsequent immune-mediated inflammation of the endothelium
  - Endothelial inflammation can be due to the natural infection with CAV-1 or, historically, was related to vaccination with the attenuated strain
  - 'Blue eye' may be unilateral, or bilateral
  - There are anecdotal reports of sporadic cases of 'blue eye' encountered following vaccination with CAV-2 strains
- Malignant catarrhal fever (MCF) (Fig. 8.32)
  - MCF is a bovine disease with high mortality that is caused by alcelaphine herpesvirus-1 or ovine herpesvirus-2
  - Corneal edema associated with endothelial cell inflammation is a feature of both African Wildebeest-associated MCF and American Sheep-associated MCF.

CORNEAL NEOPLASIA

Canine corneal squamous cell carcinoma in dogs with chronic keratitis (Figs 8.33, 8.34)

- Corneal neoplasia is relatively uncommon in dogs
- There are 28 cases of squamous cell carcinoma (SCC) or carcinoma-*in-situ* in dogs in the COPLOW collection
- Affected dogs in our series have a history of chronic keratitis
- Most cases are in brachycephalic breeds and Pug dogs are the most frequently affected.
- Affected dogs are typically middle-aged and older
- Most are low-grade carcinoma or carcinoma-*in-situ*, involving predominantly the axial cornea.
- Morphologic features in these cases include:
  - A raised mass lesion in the axial cornea
  - Abrupt margins between a well-organized epithelium, with no dysplastic or anaplastic features, and the raised mass with disorganization, dysplastic epithelial features and cellular features of anaplasia
    - If the neoplastic features are entirely contained by the basal lamina and do not infiltrate the stroma, these are carcinoma *in situ*
    - If the neoplasm invades the stroma then it is considered squamous cell carcinoma
  - In almost all cases the neoplastic tissue is confined to the superficial stroma and lamellar keratectomy, with or without adjunctive therapy, is usually a successful treatment.

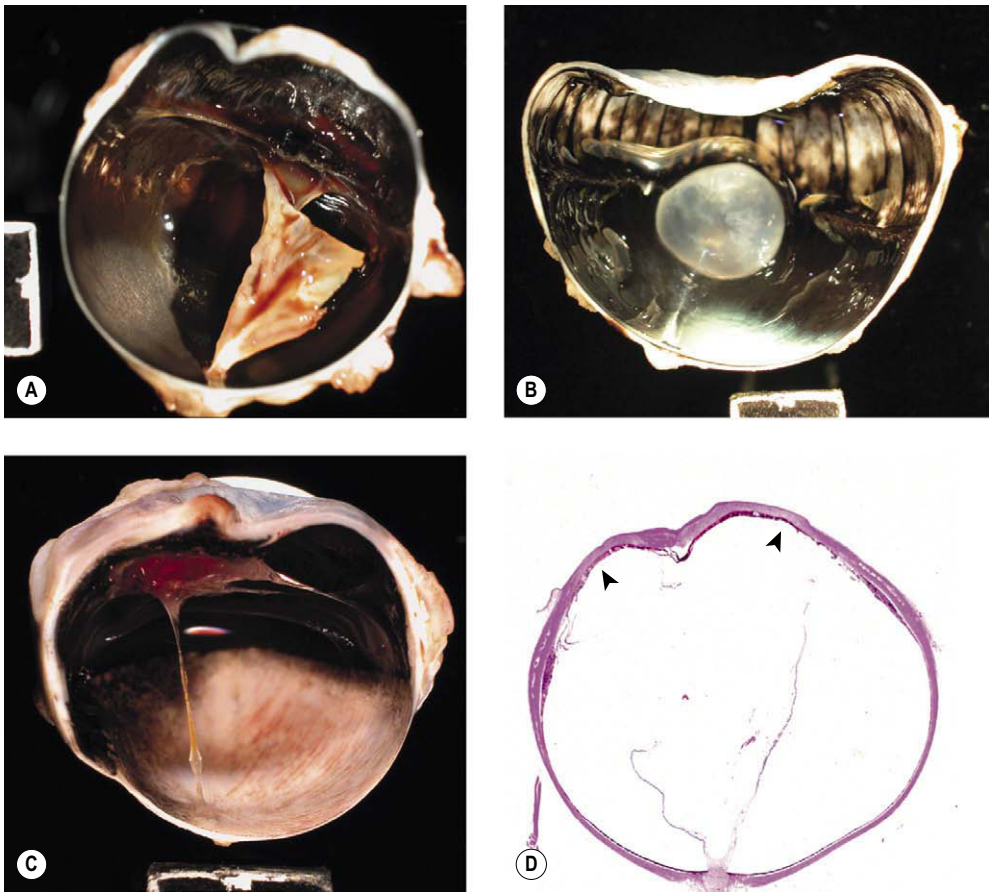


Figure 8.30 Anterior chamber collapse syndrome. (A–C) Gross photographs of animals with anterior chamber collapse syndrome resulting from early life ocular trauma. The iris tissue is plastered against the posterior cornea obliterating the anterior chamber. (D) Subgross photomicrograph of a similar globe showing pigmented iris tissue plastered against the posterior cornea (arrows).

Equine stromal-invasive squamous cell carcinoma (Fig. 8.35)

- There are eight cases of equine stromal-invasive SCC in the COPLOW collection
- This neoplasm is a variant of a limbal conjunctival SCC (discussed in detail in Ch. 7) which infiltrates primarily into the corneal lamellar stroma, masquerading clinically as chronic stromal/interstitial keratitis
- Clinically, there is a progressive thickening and opacification of the affected stroma
- Although the majority of the neoplasm lies within the corneal stroma, in some cases tumor tissue may also be recognized in the peripheral corneal surface and/or the limbus.

Angiokeratoma (vascular endothelial cell tumor arising within the cornea) (Fig. 8.36)

There are rare cases of tumors of vascular endothelial origin arising within the cornea. The COPLOW collection has one case in a horse and one in a dog.

- Infiltration of the cornea by an adjacent limbal conjunctival vascular endothelial mass was not definitively excluded in either case, as serial sections were not examined
- The other possible mechanism by which these tumors might arise would be neoplastic transformation of new vessels associated with pre-existing corneal disease.

Canine viral papilloma (see Ch. 7)

- Young dogs are affected
- Occasionally the disease is limited to the cornea.

Epitheliotropic lymphoma

There are two cases of epitheliotropic lymphoma of the cornea in dogs in the COPLOW collection.

Comparative Comments

- Overall, corneal tumors in man are unusual
- Squamous cell carcinomas can present as a primary corneal tumor, and the cornea may be involved by pagetoid spread of sebaceous carcinoma from the eyelid
- Biopsies showing corneal intraepithelial neoplasia occasionally come to the eye pathology laboratory
- Although primary melanomas of the cornea have been reported, corneal invasion by malignant melanoma of the conjunctiva is more often seen.

DISEASES OF THE SCLERA

Staphyloma (Fig. 8.37)

There are 72 cases in the COPLOW collection.

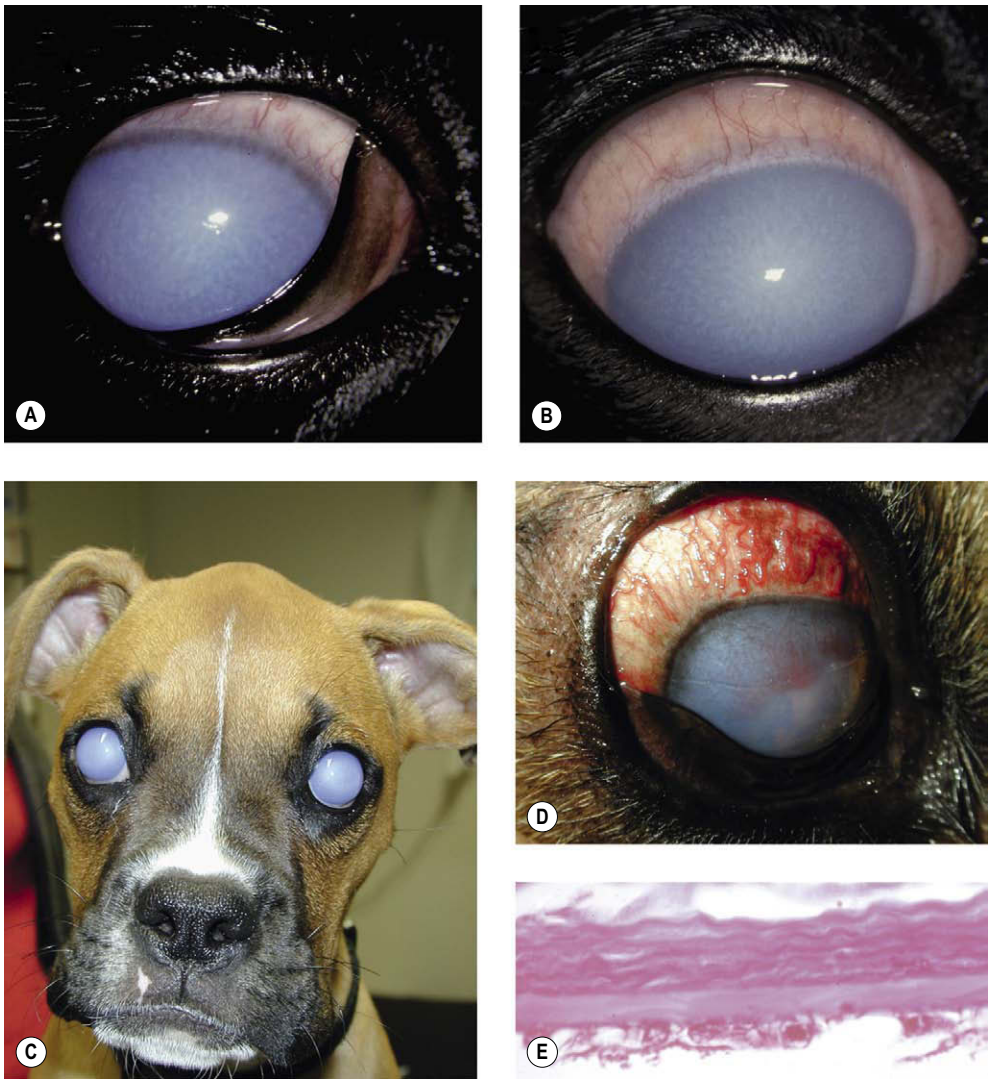


Figure 8.31 Canine 'blue eye'. (A) Boston Terrier, 7 weeks old: canine adenovirus type 2 vaccine resulted in severe endotheliitis and edema. (B) Golden Retriever, 8 weeks old: canine adenovirus type 1 vaccine initiated this case. (C) Boxer, 4 months old: canine adenovirus type 2, bilateral disease. (D) Adult dog with a more profound scleral injection. (E) Photomicrograph showing the disrupted and degenerate corneal endothelium.

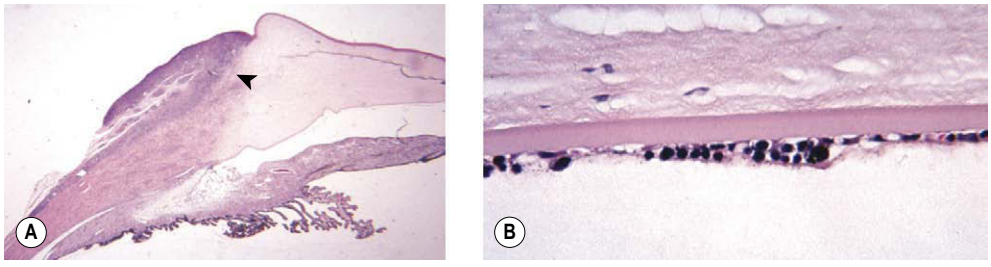


Figure 8.32 Malignant catarrhal fever. (A) Low magnification photomicrograph showing basophilic lymphocytic infiltrate (arrow) in the episclera near the limbus of a moose with malignant catarrhal fever. (B) Photomicrograph showing the corneal endothelium from the same moose with a lymphocytic infiltrate disrupting the cells (endotheliitis).

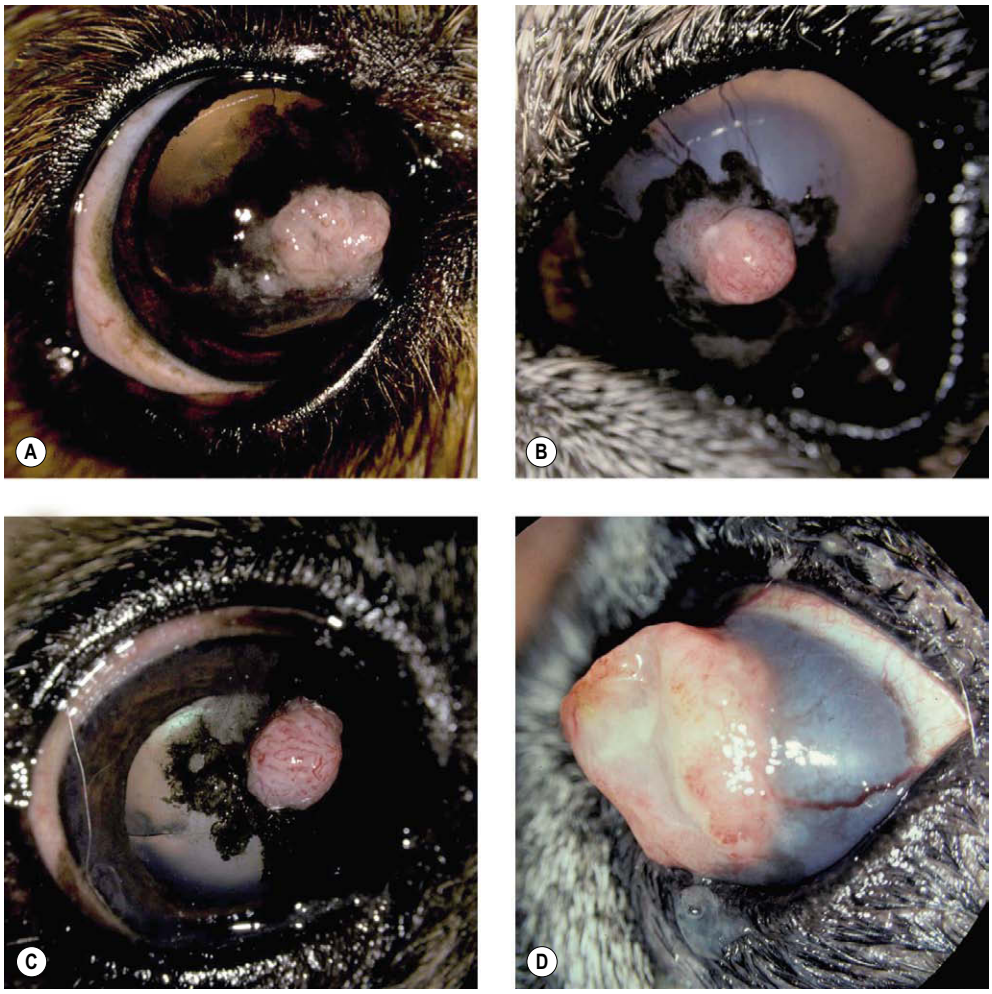


Figure 8.33 Canine corneal squamous cell carcinoma, clinical. (A) Cavalier King Charles Spaniel, 10 years old: the elevated axial mass is in an area of corneal pigmentation associated with dry eye. (B) Pug, 11 years old: the axial mass is associated with exposure keratitis. (C) Pug, 11 years old: the paraxial mass is located in the center of the pigmented cornea. (D) Pug, 12 years old: this large mass is associated with dry eye and corneal vascularization.

- A partial or full thickness defect in the cornea or sclera lined by protruding uveal tissue
- Staphyloma, may occur as a congenital lesion in isolation but is more frequently associated with other congenital ocular defects, as discussed previously, in Chapter 3.
- Acquired staphyloma:
  - Limbal staphyloma is frequently recognized in glaucomatous canine eyes (see Ch. 13)
    - In our collection, affected globes are always heavily pigmented
    - Dogs with glaucoma as a result of ocular melanosis are particularly prone to developing staphylomas
    - The relationship between scleral thinning and ocular melanosis is not known
    - The appearance of staphyloma is often mistaken for that of a neoplasm
  - Staphyloma associated with scleritis (see below).

Granulomatous scleritis, necrotizing scleritis (Figs 8.38, 8.39)

There are 93 cases of granulomatous scleritis documented in the COPLOW collection.

- All but three of these are canine cases, and most were diagnosed in enucleated globes
- The other three cases involved one cat and two birds
- Granulomatous scleritis can arise by extension of a nonspecific inflammatory process, e.g., orbital cellulitis or panophthalmitis. However, in these 93 canine cases, the diagnosis implies a specific destructive inflammation within the sclera
  - Although, in humans, granulomatous scleritis is often seen in individuals with other autoimmune conditions such as rheumatoid arthritis, this has not been a consistent feature of reported canine cases
    - No such relationship with documented autoimmune conditions has been seen in any of the cases in the COPLOW collection
  - Necrotizing scleritis has been reported in dogs with Ehrlichiosis
- Clinical features of scleritis may include:
  - Redness
  - Variable degrees of ocular pain
  - Mild exophthalmos
  - Signs of secondary uveal inflammation
  - Posterior segment lesions, e.g., retinal detachment
- The inflammation in scleritis always has a pronounced, granulomatous component characterized by the presence of histiocytes/tissue macrophages. In addition, there may be a suppurative component, i.e. necrotizing scleritis, or in chronic scleritis, a lymphoplasmacytic component may predominate

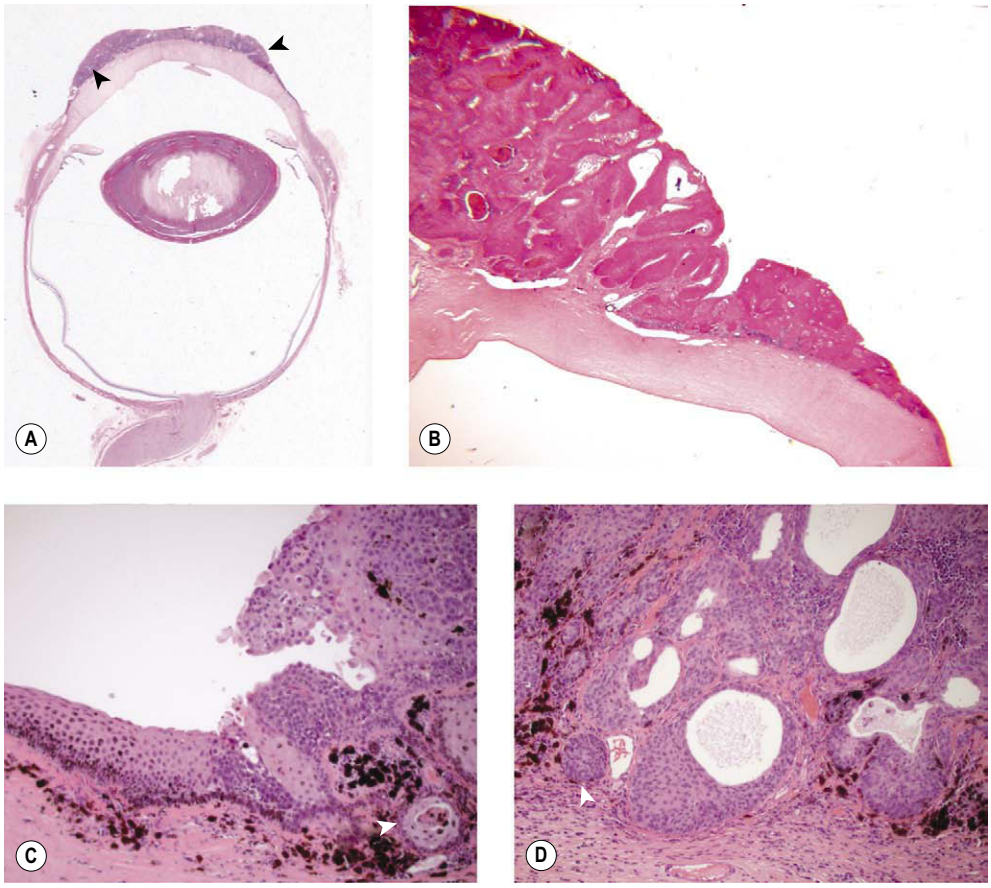


Figure 8.34 Canine corneal squamous cell carcinoma, pathology. (A) Subgross photomicrograph of a canine globe showing a superficially oriented central corneal squamous cell carcinoma (arrows). (B) Low magnification photomicrograph showing the marked thickening of the affected epithelium, but little invasion of the deep corneal stroma. (C,D) Photomicrographs of canine corneal squamous cell carcinoma showing only minimal epithelial invasion (arrows), as well as pigmentation characteristic of the chronic inflammatory disease.

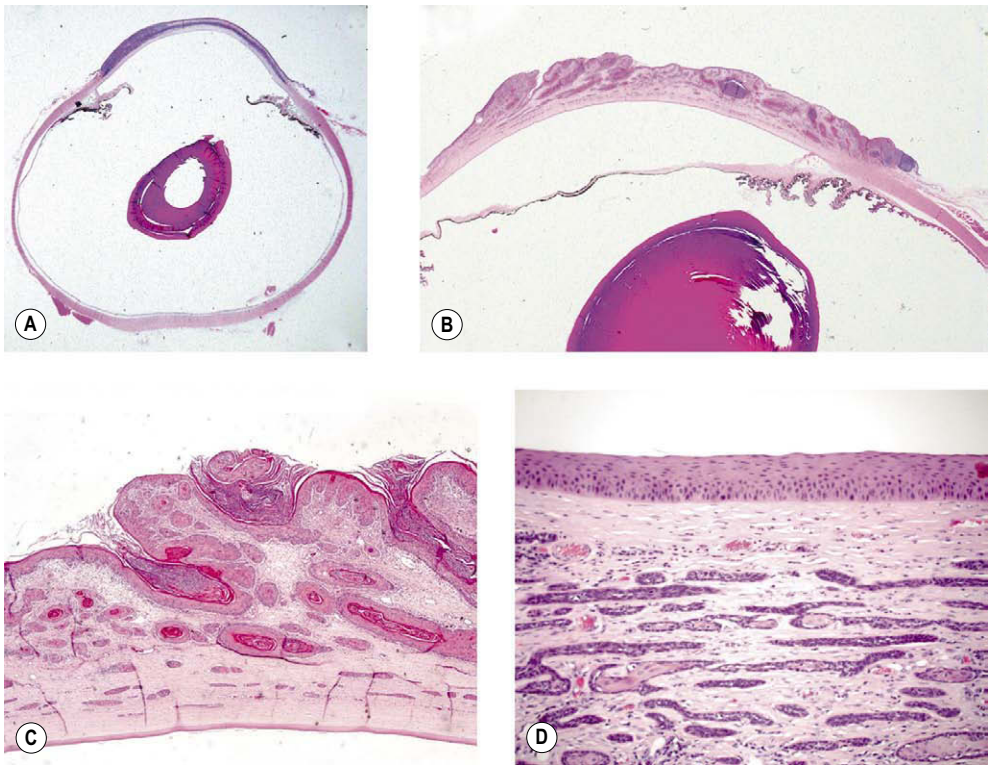


Figure 8.35 Equine stromal invasive squamous cell carcinoma. (A) Subgross photomicrograph showing an equine globe with stromal invasive squamous cell carcinoma infiltrating the lamellar stroma (blue). (B) Low magnification photomicrograph showing a similar degree of involvement as (A), but with a little more surface disruption. (C) Tumor, folded on the surface, extends into the lamellar stroma of the cornea. (D) An intact and smooth surface epithelium with neoplastic cords of epithelium within the lamellar stroma.

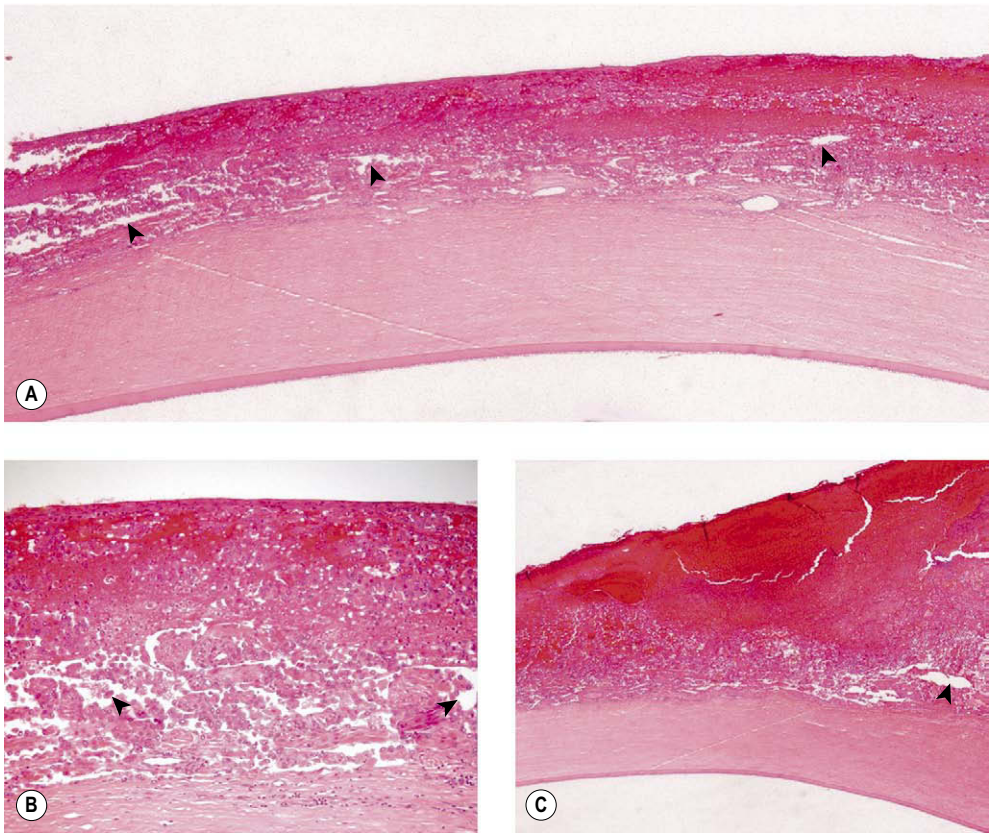


Figure 8.36 Equine angiokeratoma. (A) Low magnification photomicrograph of cornea showing invasion of the stroma by neoplastic vascular channels in equine angiokeratoma. (B,C) Photomicrographs showing similar involvement in another horse. Arrows show vascular channels.

- A diagnosis of scleritis implies that the second eye is at risk of developing scleritis
  - The clinician should be alerted to this important prognostic information, due to the potentially serious implications for vision
- The morphologic features of scleritis in dogs include:
  - The affected area of sclera is usually thickened
    - The thickened sclera is typically a solid white. These affected regions are infiltrated by granulomatous inflammation
    - Any portion of the sclera may be involved
  - More rarely, scleral thinning may occur. In these cases dramatic staphylomas may be recognized
    - Scleritis with staphyloma is usually manifest by a lymphocyte rich infiltrate with fewer granulomatous foci
  - Histologic features of scleritis include:
    - Granulomatous inflammation
    - Lysis or separation of scleral collagen
    - Granulomatous vasculitis, which is a common but not universal feature.

Canine limbal melanocytoma (Figs 8.40, 8.41)

In the COPLOW collection, there are 214 cases of canine limbal melanocytoma, representing 4% of all canine neoplastic submissions and 10% of all canine tumors of melanocytic origin.

- German Shepherd dogs are over-represented and Labrador Retrievers are weakly over-represented in the COPLOW collection.
  - Based on inter-relatedness of affected dogs in one published study, a genetic predisposition to the development of ocular melanoma has been proposed for Golden and Labrador retrievers
- There is a small spike in occurrence in dogs less than 2 years old
- Limbal melanocytomas in dogs are almost always benign but they can be quite large
- Morphologic features of limbal melanocytoma include:
  - They arise from the melanocytes which form a pigmented ring around the limbal sclera in normal, pigmented dogs
  - Limbal melanocytoma is usually a solid mass that is composed of a uniform population of heavily pigmented round cells, with very few heavily pigmented spindle cells
  - Often, biopsy samples submitted are made up of small fragments because the tumors are often just sampled for diagnostic purposes prior to cryosurgery or photocoagulation.

Feline limbal melanocytoma (Fig. 8.42)

- In the COPLOW collection, there are 46 cases of feline limbal melanocytoma, representing 1.7% of all feline neoplastic submissions and 3% of all feline tumors of melanocytic origin
- Feline limbal melanocytomas are believed to be benign
  - However, apparent generalized metastatic disease has been reported in one cat following resection of limbal melanoma
- It is important to distinguish limbal melanocytoma from extra-ocular extension of uveal melanoma, or conjunctival melanoma (see Chs 9 and 7, respectively, for further discussion of these important differential considerations)

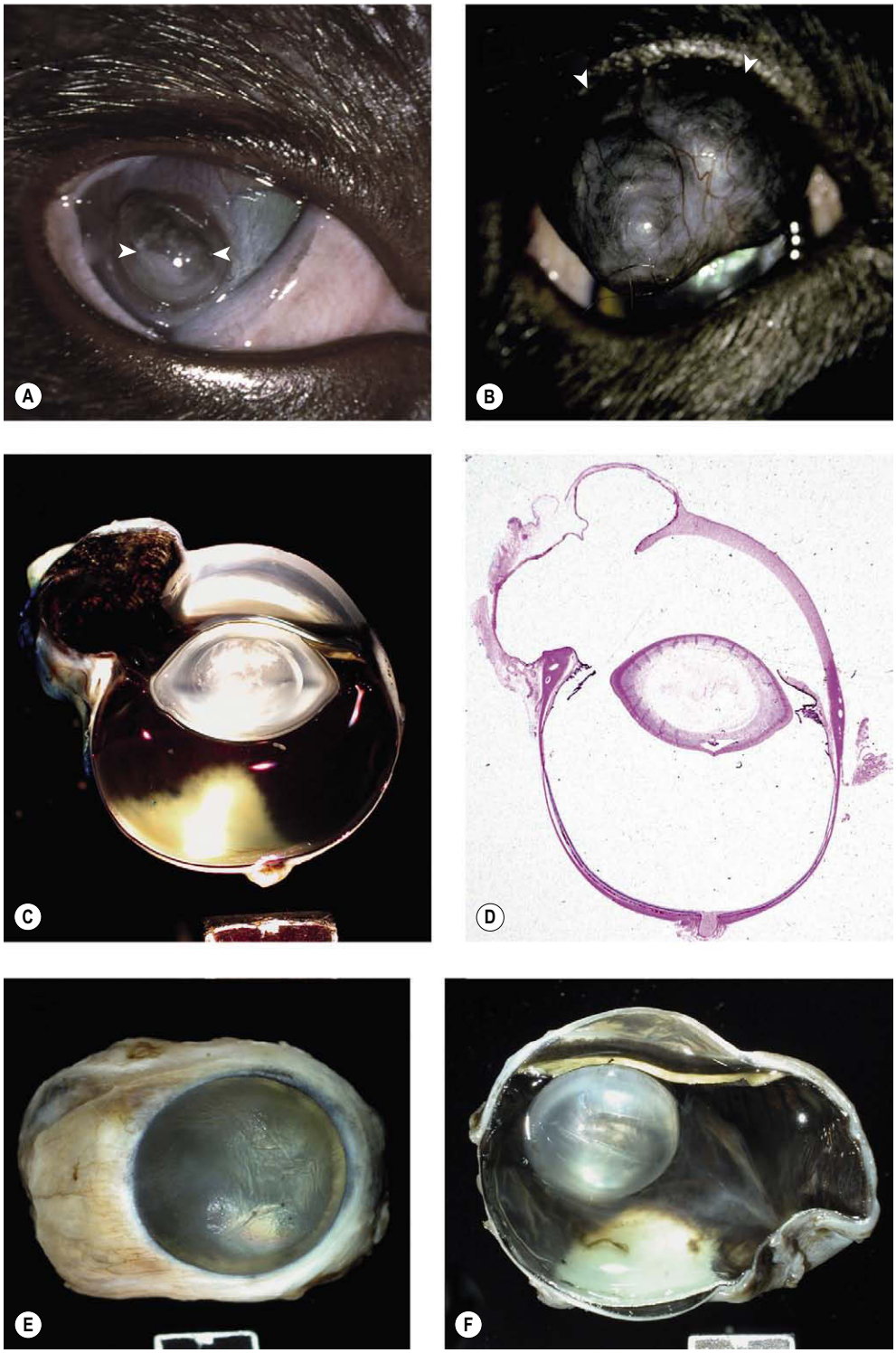


Figure 8.37 Acquired staphyloma. (A) DSH, 5 years old: iris and endothelial pigment is present in the elevated area between the arrows. (B) DSH, 6 years old: the large staphyloma (between arrows) originated from under the superior lid. (C,D) Gross photograph and subgross photomicrograph showing the same peripheral corneal and limbal staphyloma as (B). (E,F) Gross photographs showing an equatorial scleral staphyloma in a canine globe.

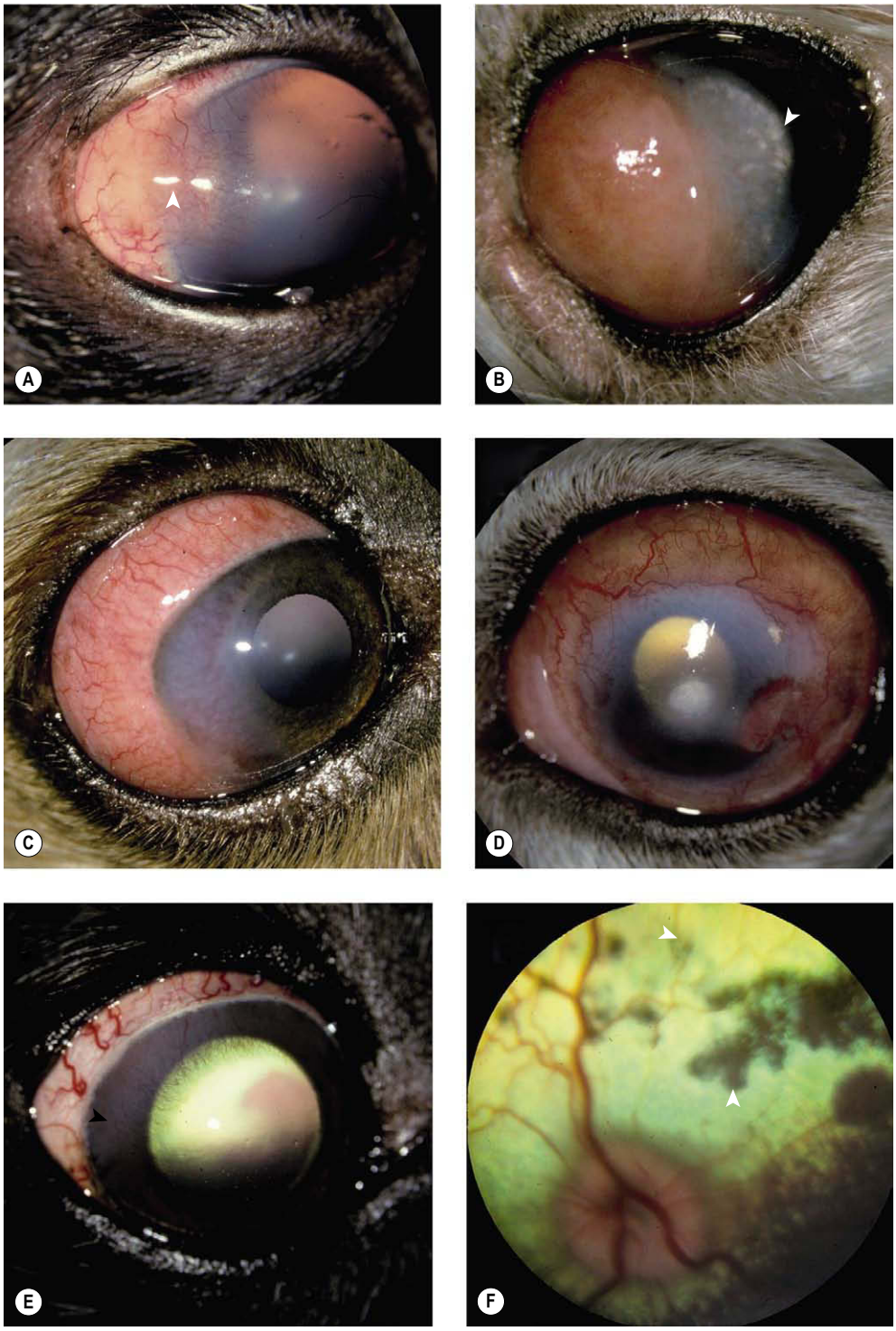


Figure 8.38 Scleritis, clinical. (A) Dachshund, 12 years old: the arrow points to the corneal side of the limbus, where vessels and inflammatory cells resulted in the limbal elevation. (B) Maltese, 5 years old: the severe nasal infiltrate is also associated with corneal lipidosis at the arrow. (C) Cocker Spaniel, 4 years old: the sclera is thickened and injected. Only edema and thin vessels are present on the cornea. (D) Cocker Spaniel, 7 years old: all scleral surfaces are severely elevated and injected. The inflammatory reaction has extended onto the cornea, obscuring the limbus. (E) German Shepherd Dog cross, 5 years old: scleral vessels are injected. The cornea at the limbus is edematous and vascularized (arrow). (F) The tapetal fundus of the dog in (E). The optic disc is swollen. Areas of abnormal tapetal pigmentation represent inflammation of sclera, choroid and retina (arrows).

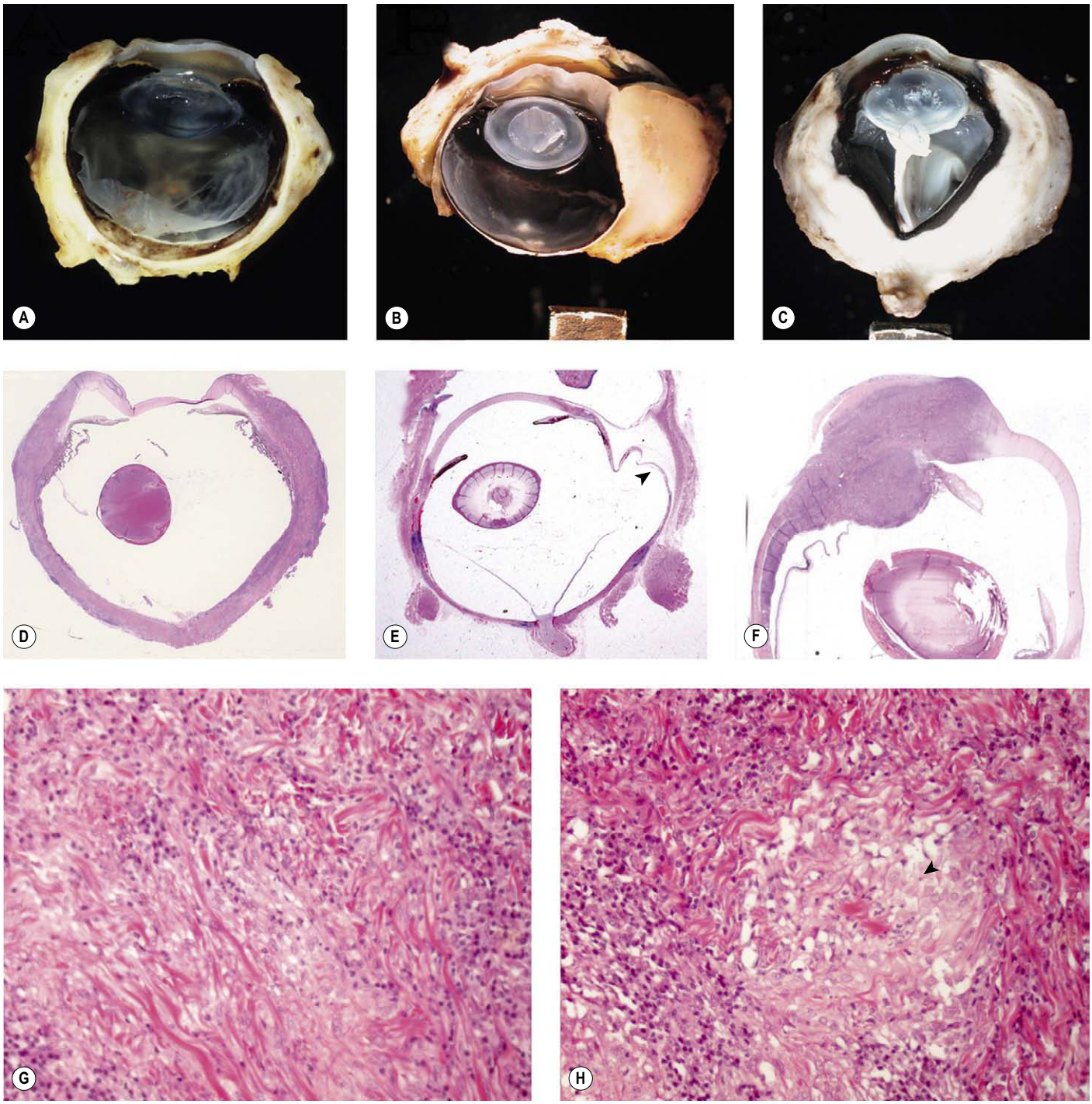


Figure 8.39 Scleritis, pathology. (A–C) Gross photographs of canine globes showing segmental or diffuse scleral thickening associated with granulomatous scleritis. (D–F) Subgross photomicrographs of canine globes showing scleral infiltration. (E) Segmental scleral thinning (arrow) and staphyloma, a rarer manifestation of granulomatous scleritis. (G) Photomicrograph showing typical granulomatous reaction in scleritis. Granulomas surround collagen fragments. (H) Highlights vasocentric granuloma (arrow).

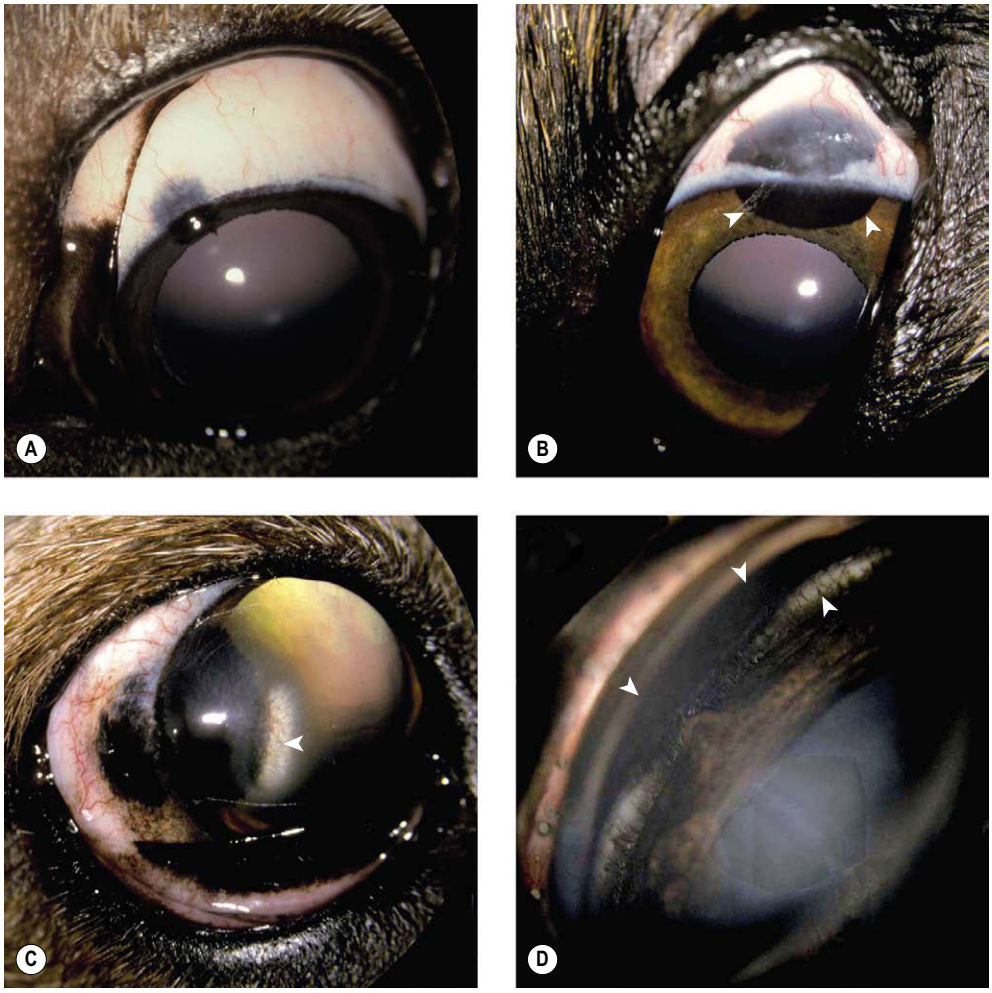


Figure 8.40 Canine limbal melanocytoma (limbal shelf melanocytoma), clinical. (A) Golden Retriever, 4 years old: this small mass extended minimally into the cornea. (B) German Shepherd Dog cross, 5.5 years old: the arrows show the extent of the tumor into the cornea. (C) Golden Retriever, 9 years old: the arrow points to the associated corneal lipidosis. The corneal involvement lies between this lipid and the scleral mass to the left. (D) Labrador Retriever, 6 years old: the gonioscopic photograph shows the corneal involvement of this extensive tumor (arrows).

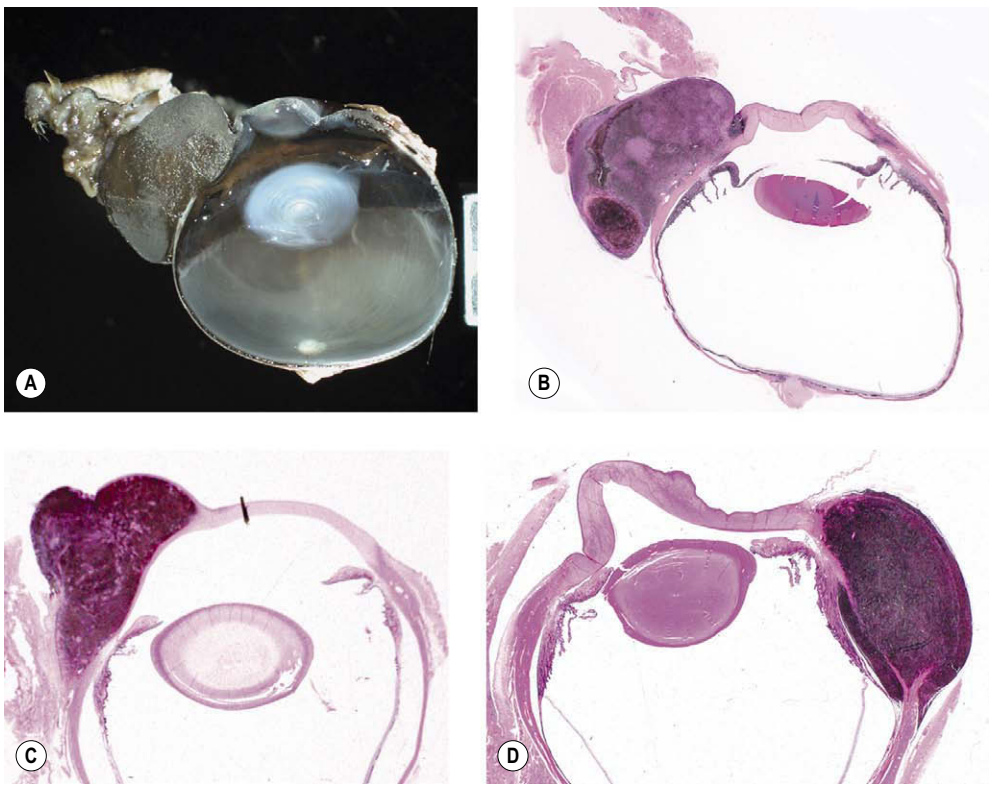


Figure 8.41 Canine limbal melanocytoma, pathology. Gross photograph (A) and subgross photomicrographs (B–D) showing canine globes with limbal melanocytoma. There is outward growth but minimal extension into the globe.

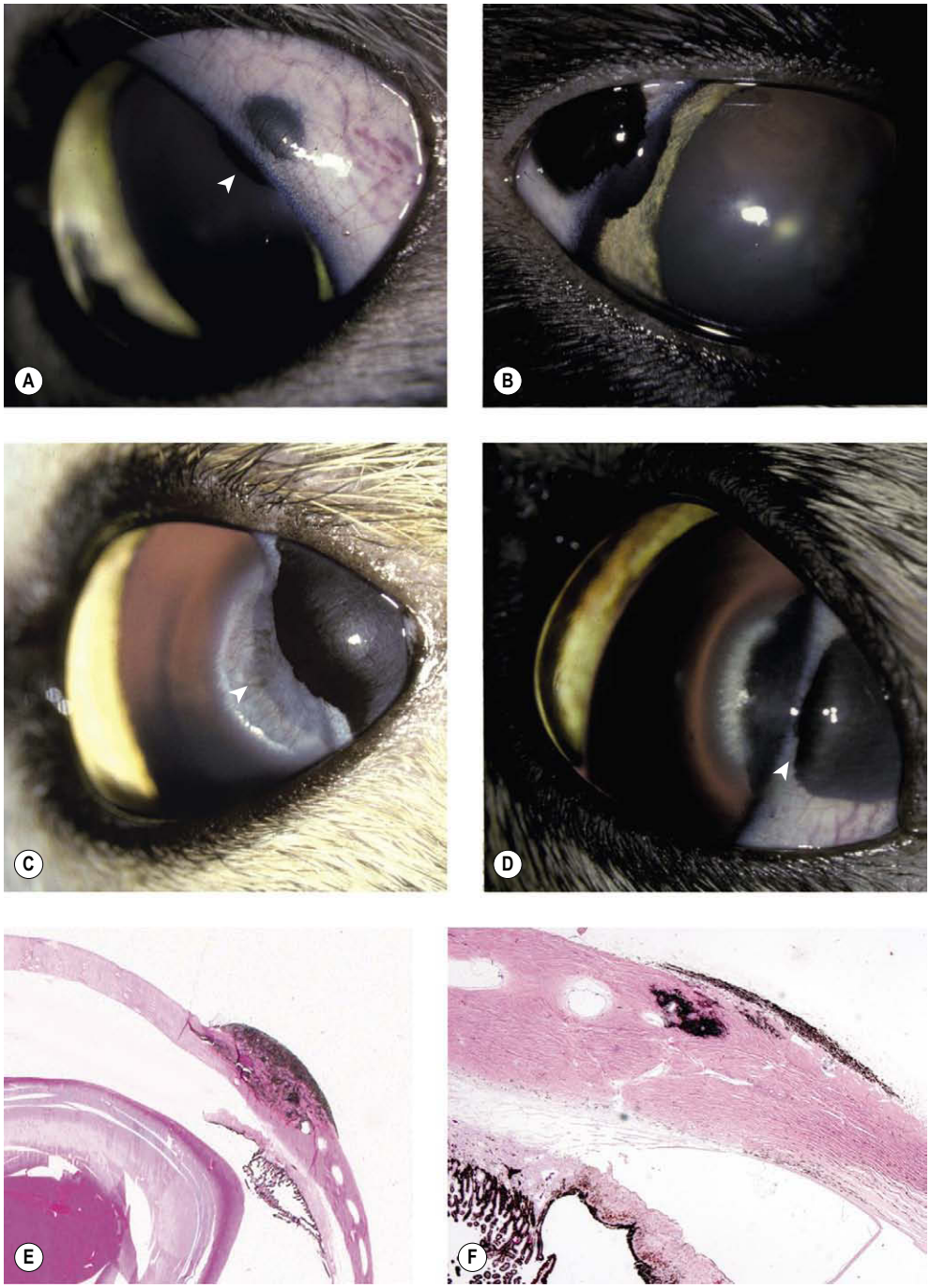


Figure 8.42 Feline limbal melanocytoma. (A) DSH, 9 years old: the arrow points to the mild extension into the cornea. (B) DSH, 12 years old: the limbal pigment mass is elevated and extends into the cornea. (C) DSH, 10 years old: the corneal involvement can be seen below the lipidosis at the arrow. (D) DSH, 9 years old: the arrow points to the normal sclera still present between the pigmented mass and the cornea. (E) Low magnification photomicrograph showing a characteristically small feline limbal melanocytoma. (F) Higher magnification showing minimal melanocytic infiltrate characteristic of feline limbal melanocytomas.

- Morphologic features include:
  - An almost pure population of heavily pigmented round cells, similar to that observed in canine limbal melanocytomas.

Comparative Comments

The major disorder of the sclera dealt with in human ophthalmology is scleritis, generally considered an idiopathic autoimmune disease.

- Scleritis may occur in isolation, or may occur in association with systemic diseases
- Rheumatoid disease is most commonly linked to scleritis, but a number of other conditions, including systemic lupus, erythematosus, polyarteritis nodosa, Wegener's granulomatosis, relapsing polychondritis, and Reiter's syndrome have been associated with it
- Scleritis in humans is subdivided into the following categories:
  - Anterior scleritis, which may be further characterized as necrotizing or non-necrotizing
  - Episcleritis, a milder disease, must be differentiated from anterior scleritis, since the etiology and management differ.
  - Posterior scleritis is an inflammatory process of the sclera, posterior to the equator of the eye.

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Chapter 9

The uvea

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BACKGROUND AND NON-NEOPLASTIC DISEASES

Normal anatomy

Anterior uvea: iris and ciliary body

Iris (Fig. 9.1)

- Stroma
  - Embryologically derived from the neural crest, apart from vascular endothelium derived from mesoderm
  - Loose connective tissue stroma populated by fibroblasts and melanocytes. Melanocyte population tends to be more dense in the posterior stroma than in the anterior stroma
  - The anterior border has no epithelial surface and, therefore, there is little to deter fluid exchange with the anterior chamber
  - Capillaries are non-fenestrated, contributing to the 'blood-aqueous barrier'. However, blood vessel endothelium lacks tight junctions in many domestic animals, with permeability differing greatly between species
    - Inflammation of the iris leading to increase in vascular permeability manifests as protein in the aqueous humor. This is detectable by slit-lamp biomicroscopy as 'aqueous flare'

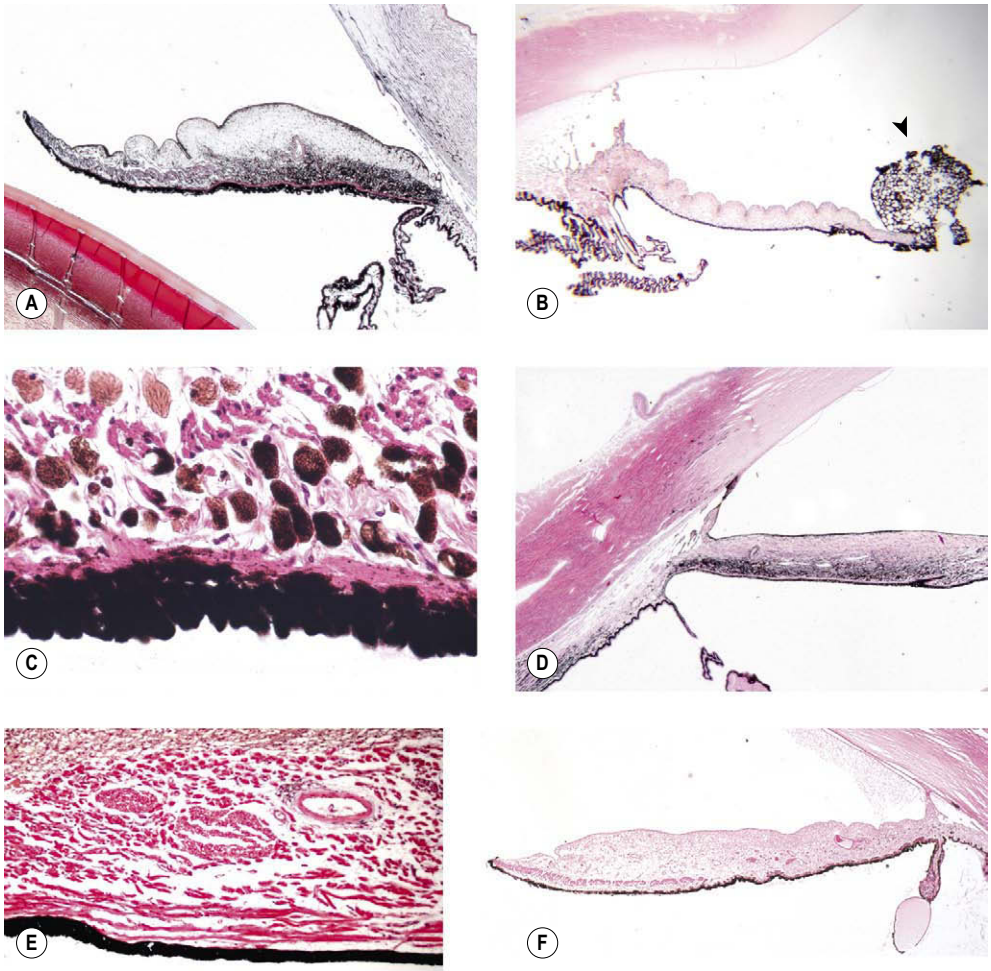


Figure 9.1 Normal anterior uvea. (A) Low magnification photomicrograph of the normal canine iris and irido-corneal angle structures. (B) Low magnification of the normal equine iris and irido-corneal angle structures including the corpora nigra (arrow). (C) Higher magnification of a normal canine iris showing the iris epithelium and dilator muscle. (D) Low magnification of the canine iris and irido-corneal angle from a normotensive dog with goniodysgenesis. (E) The highly muscular iris from a diving bird (Loon). In birds, the iridal muscle is skeletal muscle, and in this diving bird the robust iris muscle is important in accommodation. It plays a role in increasing the curvature of the anterior lens surface, thereby increasing refraction. (F) Low magnification of a canine iris with a blue eye showing the absence of melanin in the stroma even though the posterior pigment epithelium is fully pigmented.

  - The iris stroma, and for that matter the entire globe, lacks lymphatic vessels
- Muscles and posterior epithelium
  - Sphincter muscle
    - Constricts in bright light and during accommodation
    - Smooth muscle in mammals, derived from neuroectoderm of optic cup
    - Striated muscle in birds and most reptiles, in which it is predominantly of neural crest origin
  - Dilator muscle and posterior pigmented epithelium
    - The posterior epithelium and the dilator muscle together form a complex two-layered structure derived from the neuroectoderm of the anterior optic cup
    - The posterior, pigmented epithelium of the iris is continuous posteriorly with the inner, non-pigmented epithelium of the ciliary body
    - The myoepithelial cells of the anterior iris epithelium are among the most complex cells of the body. Basally, their cytoplasm is contractile (the dilator muscle) and apically the cytoplasm of these epithelial cells contains melanin granules. The anterior iris epithelium is continuous with the pigmented epithelium of the ciliary body
    - In birds and most reptiles, as with the constrictor muscle, the dilator muscle is striated, although smooth muscle often also plays a role in pupil dilation
  - Granula iridica (corpora nigra)
    - In domestic herbivores such as equidae, bovids, and camelids, the iridal epithelia at the superior margin of the pupil, and sometimes also at its inferior margin, gather and expand anteriorly to form prominent pigmented nodules or, in the case of the New World Camelids, well-organized pleats
    - The postulated role of the granula iridica is to shade the structures of the inner eye from ambient sunlight from above, much like the bill or visor of a baseball cap

Ciliary body (Fig. 9.2)

- The ciliary body is continuous anteriorly with the base of the iris. The structure and function of the aqueous outflow pathways will be addressed in Chapter 13, given their importance in the pathology of glaucoma
- The ciliary body is divided into an anterior pars plicata, characterized by a series of meridional folds or processes, from which the suspensory zonules of the lens originate, and a posterior pars plana. The structure of the ciliary processes, in terms of their topography and angio-architecture differs considerably between mammalian species, and in non-mammalian vertebrates distinct ciliary processes may be absent
- The stroma and the ciliary muscle
  - The supraciliary space is a potential space between the sclera and ciliary body and is continuous posteriorly with the

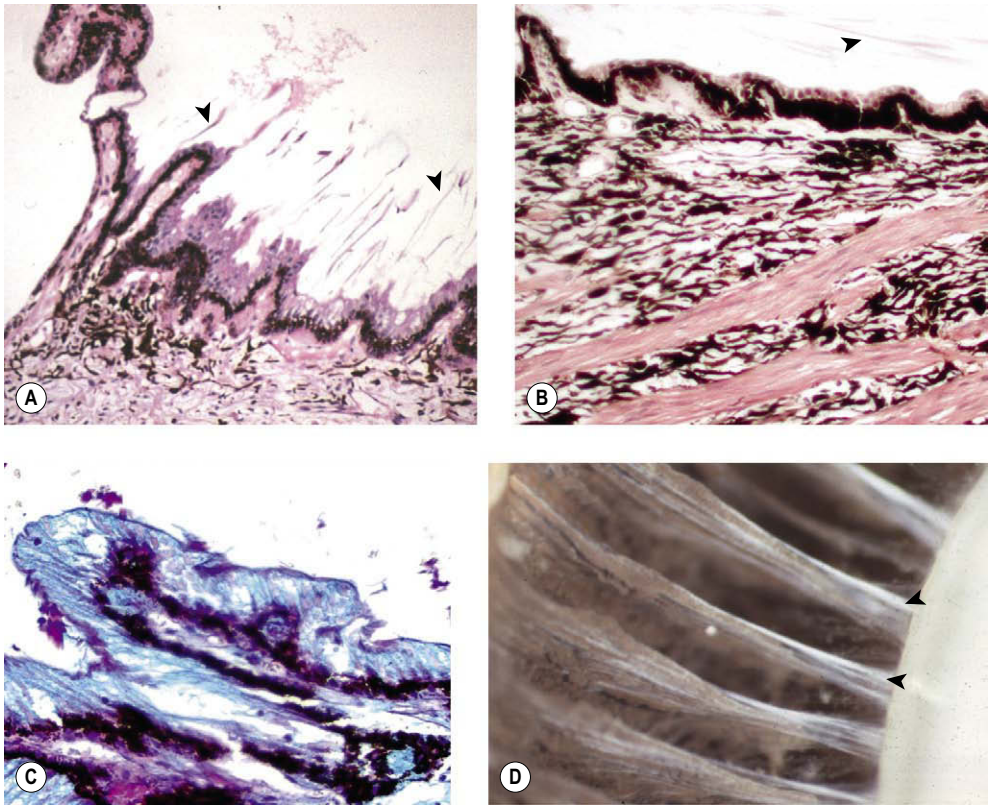


Figure 9.2 Normal ciliary body. (A,B) Photomicrographs of the canine ciliary body pars plicata showing the inner non-pigmented epithelium, the pigmented epithelium, and the zonular ligaments (arrows). (C) Canine ciliary body epithelium, stained with Alcian blue PAS, showing the secretion of hyaluronic acid in blue. (D) Dissecting microscope image of the canine lens suspensory apparatus showing normal zonular ligaments. The formalin-fixed globe was post-fixed in glacial acetic acid, which helps to opacify the zonular ligaments fibers (arrows).

suprachoroidal space. The supraciliary and suprachoiroidal space play a role in the uveoscleral or unconventional pathway of aqueous outflow. This space becomes prominent when exudates or hemorrhage accumulate in the uvea, particularly inferiorly due to the additional influence of gravity
  - The stroma of the ciliary body contains the ciliary muscle, or the muscle of accommodation
    - The ciliary muscle is derived from neural crest tissue
    - The ciliary muscle is smooth muscle in mammals and striated in birds and most reptiles
    - The ciliary body vasculature is highly permeable, with fenestrated capillaries, thus making no functional contribution to the blood-aqueous barrier
- The ciliary body epithelium
  - The ciliary body epithelium is a two-layered epithelium derived from neuroectoderm of the optic cup
    - The cells of these two mono-layers are oriented apex-to-apex
    - The inner epithelium is non-pigmented except immediately adjacent to the iris epithelium, where it may contain pigment
    - Ciliary epithelium actively secretes aqueous humor against a pressure gradient
    - The ciliary epithelium secretes extra-cellular matrix proteins which assemble to form the zonular ligaments suspending the lens
    - The ciliary epithelium secretes hyaluronic acid which provides substance to the vitreous body
  - Inner, non-pigmented ciliary epithelium
    - Junctional complexes in the apico-lateral membranes of the inner, non-pigmented epithelial cells represent the ciliary body's contribution to the functional blood-aqueous barrier. Disruption of this barrier by inflammation and other disease processes results in an increase in the protein content of aqueous humor, clinically detectable as aqueous flare
    - The inner epithelium is continuous with the neuro-sensory retina
    - The basal lamina of the non-pigmented epithelium forms the boundary between the ciliary epithelium and the vitreous body and the posterior chamber
      - Anatomically as well as functionally, the vitreous body and the posterior chamber both represent modified extracellular spaces and not luminal spaces. This feature is important to our understanding of how these spaces are invaded by blood vessels and spindle cells during disease states
    - The ciliary epithelium secretes hyaluronic acid. The hyaluronic acid is secreted apically and must be transported around the cell toward the vitreous body in extra-cellular 'channels' visible on Alcian blue staining
    - The inner, non-pigmented epithelium of the ciliary body is often laden with lympho-plasmacytic inflammatory cells in chronic inflammation and also in lymphoma
      - This observation leads one to speculate that the non-pigmented epithelium serves a function in immune-regulation
    - The native inner epithelium is vimentin positive and cytokeratin negative, a staining pattern which is unusual among epithelial tissues
  - The outer, pigmented epithelium
    - The basal lamina of the pigmented epithelium of the ciliary body lies at the junction with the stroma

– The outer epithelium of the ciliary body is continuous with the retinal pigment epithelium.

The posterior uvea: the choroid

The choroid (Fig. 9.3) is the vascular tunic of the posterior segment.

- It supplies vascular perfusion for the highly metabolically active and oxygen dependent outer retina via the choriocapillaris
- The choroid usually contains abundant melanocytes and serves as a pigmented lining of the rigid globe, which reduces internal light reflection and also functions as a 'sink' that traps free-radicals.

The suprachoroidal space

The suprachoroidal space is a potential space immediately adjacent to the sclera, which often expands and fills with edema, hemorrhage, or exudates in disease states. It is continuous anteriorly with the supraciliary space and plays an important role in unconventional outflow of aqueous humor.

The choroidal stroma

The choroidal stroma contains many large arteries and veins supplying blood to the choriocapillaris, a capillary bed with a very high rate of perfusion.

The choriocapillaris

- The choriocapillaris is a highly fenestrated capillary bed supplying nutrition to the outer retina
- The choriocapillaris is defined internally by Bruch's membrane, which is a multi-layered basement membrane complex formed by the basal laminae of the capillary endothelium and the retinal pigment epithelium, with variable amounts of collagen and elastin fibers.

The tapetum lucidum

- Most of the common domestic mammalian species have a highly reflective tapetum lucidum positioned between the choriocapillaris and the medium-sized vessel layer of the choroidal stroma, superior to the optic nerve head. The peak

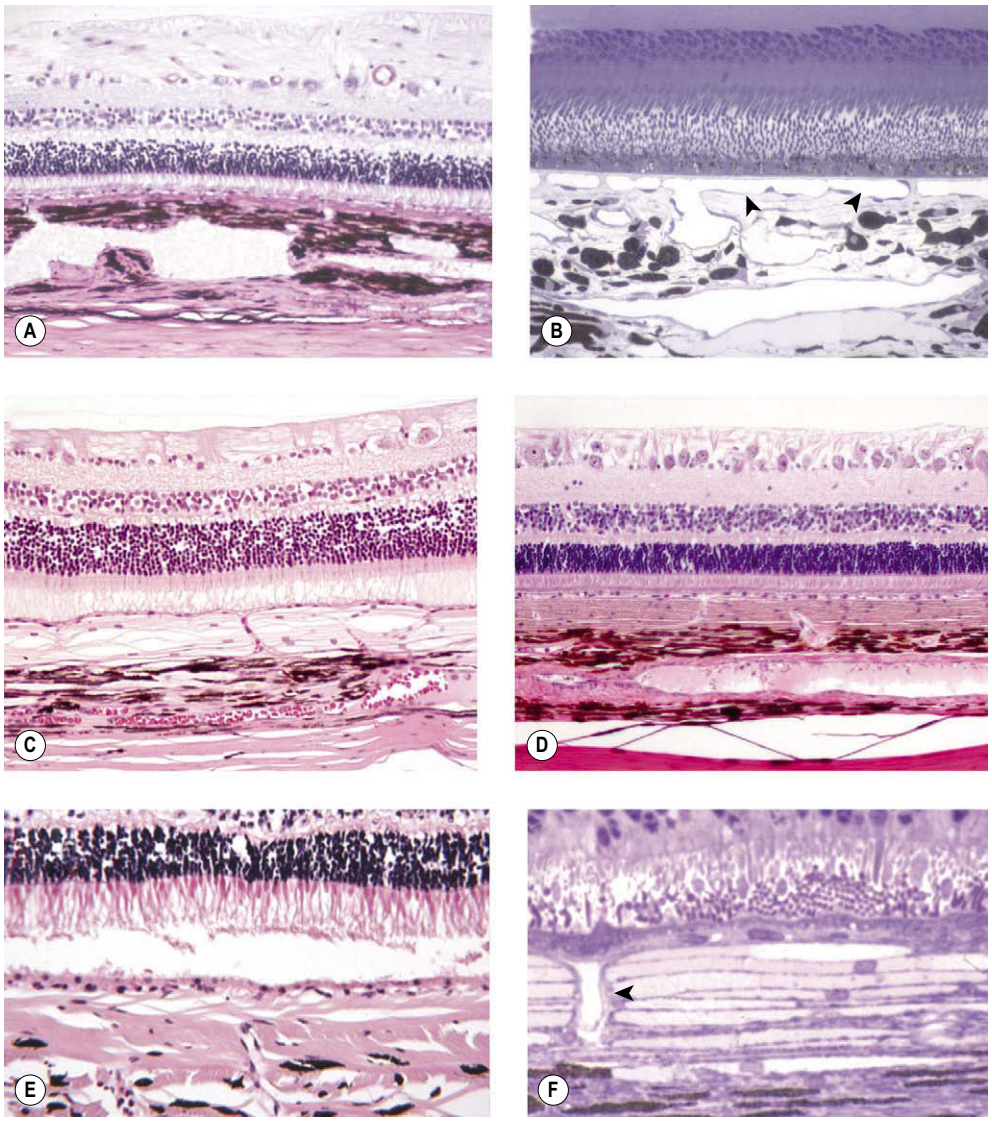


Figure 9.3 Normal choroid. (A) Photomicrograph of the normal canine retina and tapetal choroid. There is no pigment in the retinal pigment epithelium. (B) Higher magnification of a perfusion-fixed primate outer retina and choroid. The perfusion fixation makes the choriocapillaris easily appreciated (arrows). Using standard surface fixation this important vascular structure collapses and is hard to detect. (C) Photomicrograph of the canine tapetal retina and choroid showing a thicker tapetum than in (A). (D) The normal feline tapetum is thicker and has a brown tincture. (E) Fibrous tapetum from a horse. (F) Plastic section of a canine tapetum showing the characteristic parallel stacking of the tapetal cells in dogs. A blood vessel (arrow) passes through the tapetum to feed the choriocapillaris.

wavelength of the light reflected by the tapetum is thought to be tailored to that particular species' biological niche
  - The cellular tapetum
    - All carnivores have a cellular tapetum made up of regularly arranged cells. Each tapetal cell contains precisely oriented organelles (rodlets) that reflect light in the visible spectrum
      - The canine tapetum, in common with that of all carnivores except cats, has a highly variable thickness and the reflective rodlets are composed of a zinc-cysteine complex. The canine tapetum can be so thin that it may not be apparent by light microscopy and one must rely on identification of the non-pigmented RPE to determine the location of the superior fundus
      - The feline tapetum is distinct from that of the dog, in that it is consistently thicker and the reflective rods, which are more precisely oriented, are made up of a riboflavin-zinc complex. This type of tapetum is strongly autofluorescent
  - The fibrous tapetum
    - Domestic herbivores generally have a tapetum made up of cell-poor, regularly oriented layers of collagen
- The overlying retinal pigment epithelium lacks pigment in the area of the tapetum
- Penetrating vessels can be seen in cross-section to pass from the medium-sized vessel layer through the tapetum at right angles, then terminate in the choriocapillaris.

Comparative Comments

While in general terms the anatomy of the human uvea conforms to that described for other species, differences exist – some subtle and some profound. Often, when confronted with an eye from a non-human species, an ophthalmic pathologist can find distinctive clues to the identity of that species from the appearance of the iris, ciliary body, or choroid and tapetum lucidum. Although a broad class of retinal diseases in humans is referred to as tapeto-retinal degeneration, the human does not have a reflective, cellular, or fibrous tapetum lucidum positioned between the choriocapillaris and the choroidal stroma. The presence of the tapetum lucidum is always intriguing when seen by pathologists accustomed mainly to human eyes.

Congenital conditions

The morphologic features of the canine blue eye (Fig. 9.4)

- In the absence of pigment within the iris stroma, the iris color will appear blue because of the diffraction of incident light within the iris stroma. The absence of pigment is due to a genetic color diluting effect, e.g. associated with the merle gene in dogs, on melanocytes of the body that are derived from the neural crest, including those of the hair coat and the stromal tissues of the uveal tract. The lack of pigment is not always uniform. For example, in some animals only one eye is blue while the other is brown (*heterochromia irides*), or in some eyes only a portion of the iris is blue (*heterochromia iridis*)
- The iris epithelium and the retinal pigment epithelium have a distinct neuroepithelial embryological origin, and are normally pigmented
- Iris stroma is devoid of pigment but not usually significantly hypoplastic. In contrast, the choroid of affected eyes is not only devoid of melanin, but variably hypoplastic. Likewise, the tapetum is often hypoplastic or absent
- The canine blue eye contains no identifiable melanocytes in the iris stroma when stained, by immunohistochemistry, for melanocytic markers. However, premelanosomes have been described in the cytoplasm of cells presumed to be melanocytes when examined with transmission electron microscopy. Feline and human blue irides have stromal melanocytes, but their cytoplasm lacks melanosomes.

Uveal coloboma

See Collie eye anomaly and anomalies associated with merle ocular dysgenesis in Chapter 3.

Iris hypoplasia and aniridia (Fig. 9.5)

- Iris hypoplasia generally affects only iris stromal tissue and may be localized to specific zones of the iris.
  - Blue irides are most often affected, although pigmented irides may also be hypoplastic
  - Hypoplastic tissue may appear thin in cross-section, or clinically may appear to bulge anteriorly
  - In horses, zones of iris stromal hypoplasia are commonly observed superior to the pupil margin. Clinically these often appear to bulge anteriorly
- Sporadic reports of cases diagnosed clinically as aniridia generally represent examples of severe iris hypoplasia, with rudimentary iris tissue. True aniridia is very rare
  - Bilateral aniridia has been reported in horses, and in some breeds may be a familial trait
  - Aniridia is a rare, sporadic abnormality in other species, but has been documented in Llanwenog sheep in the UK
  - Dermoid, or corneal vascularization, has been reported as a concurrent finding in aniridia, often involving the superior limbus
  - Congenital cataract is also a frequent finding
- There are three equine cases of severe iris hypoplasia in the COPLOW collection.
  - All three cases in the COPLOW collection also have epithelial thickening at the limbus with hyperkeratosis but not true dermoid
  - All three cases also had concurrent cataract
- Diffuse iris stromal hypoplasia is also observed in Siamese cats with inherited congenital glaucoma (see Ch. 13)
- Hypoplasia of the iris dilator muscle, clinically appreciated as a miotic pupil, is a characteristic feature of the complex of congenital ocular anomalies seen in Rocky Mountain horses (see Ch. 3).

Persistent pupillary membranes (PPM)

- These strands of uveal tissue represent remnants of the vessels and mesenchyme of the anterior *tunica vasculosa lentis*, or pupillary membrane, a sheet that normally overlies the anterior surface of the lens during development.
  - The tunica vasculosa lentis mostly regresses by the time of birth, or within the first several weeks of life, depending on the species and their degree of ocular maturity at birth
  - PPM represent a delay in, or failure of, normal regression of the anterior tunica vasculosa lentis
- PPMs are a common incidental finding, recognized sporadically in dogs and horses. An inherited predisposition has been reported in several breeds of dog, most notably the Basenji

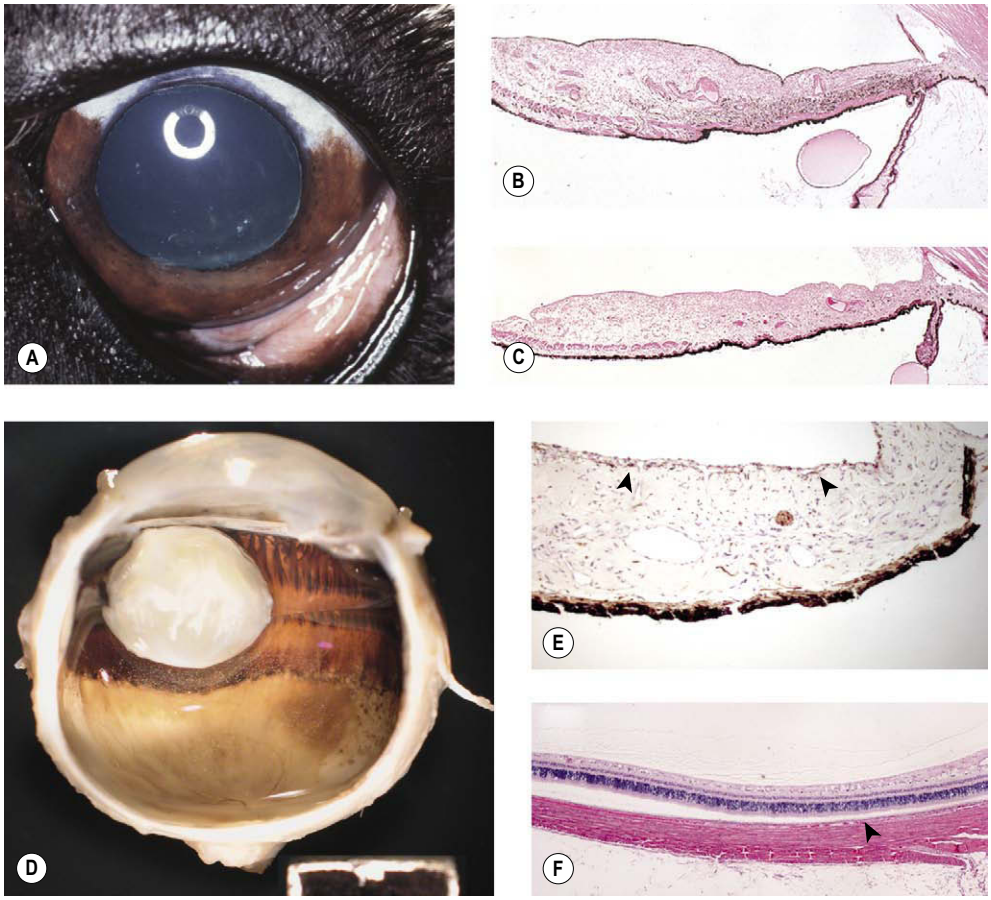


Figure 9.4 Canine blue eye phenotype. (A) Clinical photograph of a Siberian Husky eye with a partially blue iris (heterochromia iridis). (B,C) Low magnification photomicrographs, from the same eye as (A), showing pigmented side, (B), and blue side, (C). (D) Gross photograph of the globe from a blue-eyed Husky illustrates the lack of pigment in both the anterior and posterior uvea. There is still pigment in the epithelium of the iris and ciliary body and, to a lesser extent, the RPE. (E) Photomicrograph of the iris from a canine blue eye stained by immunohistochemistry for glial fibrillary acidic protein (GFAP). The image shows expected positive staining in the nerves, in the dilator muscle and around muscles. There is also a plexus of positive staining at the anterior surface (arrows) that is not seen in similarly stained brown irides. (F) Low magnification photomicrograph showing the non-pigmented and hypoplastic choroid (arrow) in a blue eye.

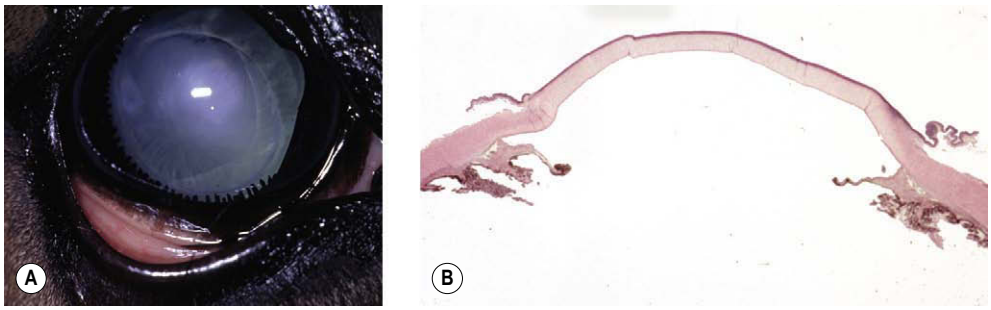


Figure 9.5 Equine iris hypoplasia. (A) Clinical photograph of a horse with iris hypoplasia. Ciliary processes are visible at the margins of the overly wide pupil. (B) Subgross photomicrograph of the eye in (A) showing the undersized irides.

- PPM may also occur in association with other lesions, including microphthalmic syndromes, and with local cataract or corneal opacity if they attach to the anterior lens capsule, or corneal endothelium respectively
- Peter's anomaly, refers to a more severe spectrum of anterior segment malformation characterized by persistent sheets of mesenchyme and corneal and lens opacities (see Ch. 3).

Degenerative, hyperplastic, and age-related conditions

Iris atrophy (Fig. 9.6)

- Iris atrophy is seen as an age-related change in several species
  - Progressive thinning of the iris stroma can lead to the appearance of 'holes' in the iris that should be distinguished from congenital iris hypoplasia or colobomas
- Atrophy can also be a feature in chronic glaucoma or after trauma.

Cysts of the irido-ciliary epithelium

- Sporadic iridal cysts (Figs 9.7, 9.8)
  - Cysts of the posterior iris epithelium may be recognized in any species, and occur commonly in dogs. They may affect any breed, being particularly common in Labrador and Golden retrievers, but are seldom of clinical significance
  - The pigmented epithelium of the iris or, less frequently, the inner epithelium of the ciliary body, undergoes spontaneous cystic hyperplasia, in the absence of inflammation or any other apparent predisposing factors



Figure 9.6 Iris atrophy. Siamese, 13 years old: the tapetal reflex can be seen in the thin temporal iris. It is especially obvious through the many iris holes.

  - Similar cystic changes may affect the iris epithelium associated with the corpora nigra in horses, and if sufficiently large, can impact vision
  - Acquired iris cysts, in cats, are a consistent morphological feature seen in eyes with a history of blunt trauma, or with other morphologic features suggestive of blunt trauma
  - Spontaneous iris cysts are more likely to be bilateral and multiple in cats than in dogs and horses
- Clinical appearance and complications of iris cysts
  - Cysts can break off and float free in the anterior chamber, although in cats they generally remain attached to the iris epithelium. Very rarely, they can move into the vitreous
  - In dogs and horses, these cysts are typically spherical or ovoid and often darkly pigmented although they may vary in their degree of pigmentation. Feline iris cysts tend to be black, or very darkly pigmented, and are often more elongated and ovoid in appearance than canine iris cysts
  - Cysts can masquerade as pigmented masses and careful clinical evaluation is essential to avoid inappropriate removal of the eye. As they are thin-walled, iris cysts can be distinguished from other pigmented masses (neoplasms) by trans-illumination using a bright light source

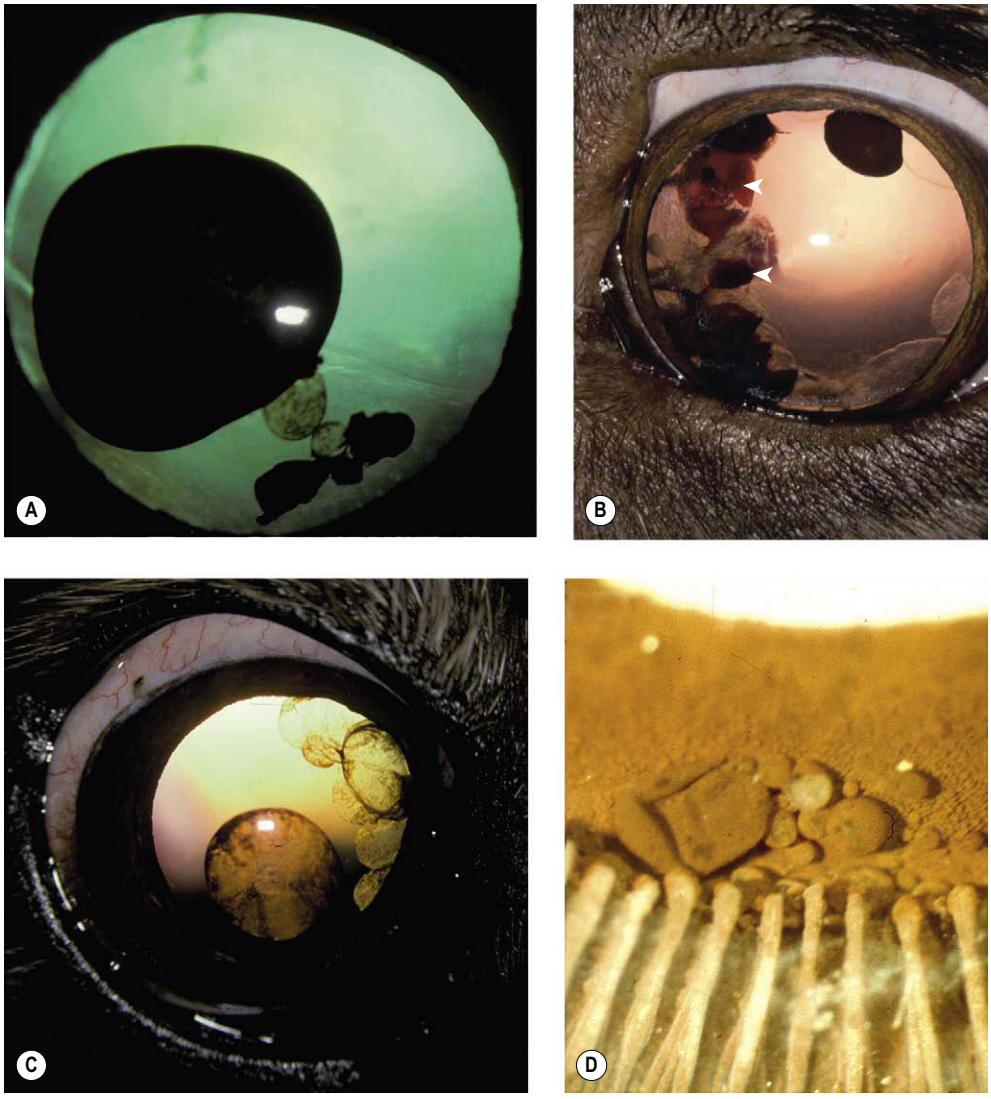


Figure 9.7 Canine iris or ciliary body cysts. (A) Boston Terrier, 11 years old: the large central cyst is adherent to the corneal endothelium. (B) Labrador Retriever, 7 years old: multiple cysts are present at the pupil margin. Several cysts are filled with blood (arrows). (C) Golden Retriever, 3 years old: both eyes had multiple cysts visible at the pupil margin. The one large translucent cyst is free floating in the anterior chamber. (D) Gross photograph taken with a dissecting microscope showing pigmented iridal cysts on a canine posterior iris.

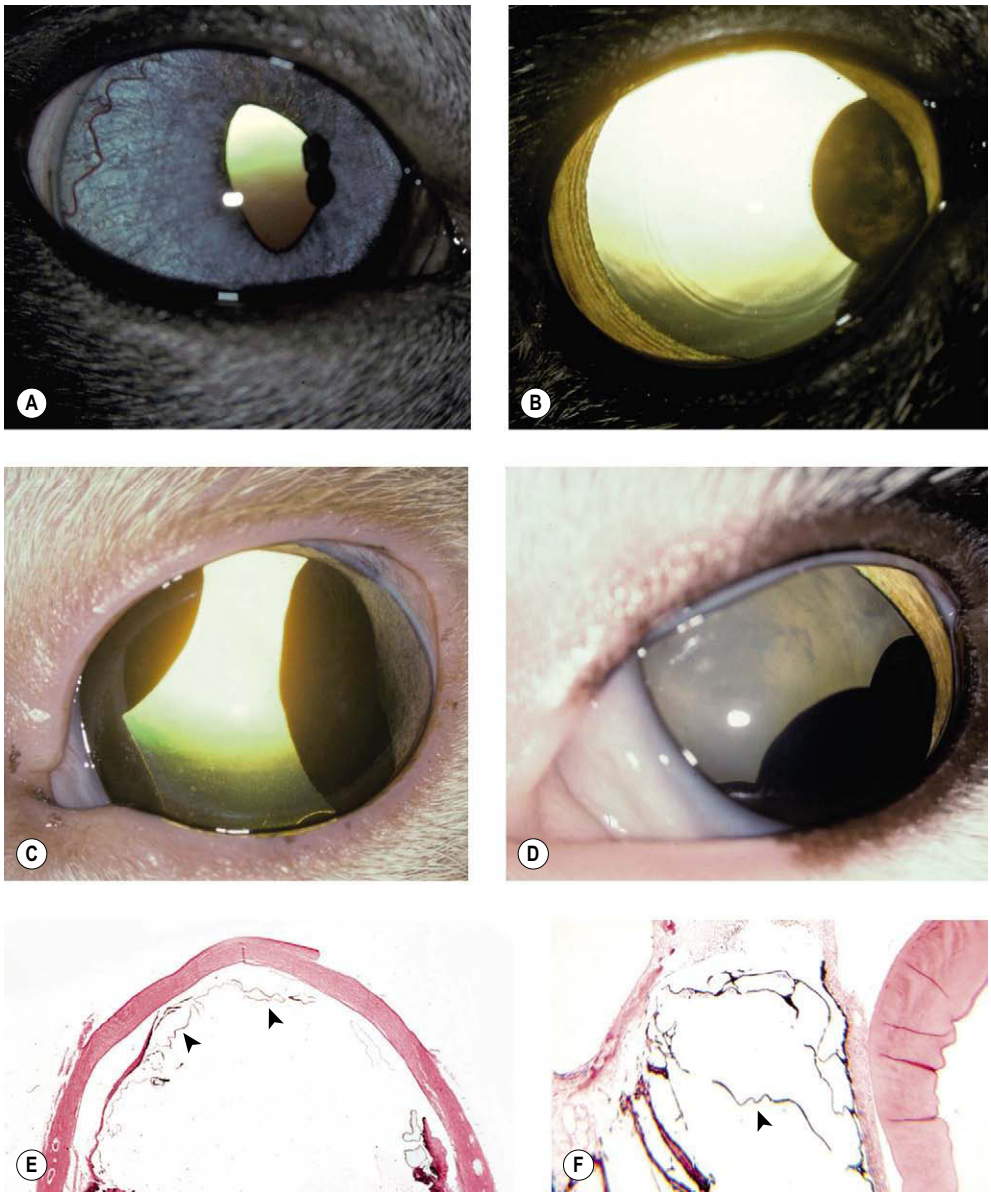


Figure 9.8 Feline iris or ciliary body cysts. (A) Siamese, 7 years old: two heavily pigmented cysts originate at the pupil margin. (B) DSH, 11 years old: a faint tapetal reflex can be seen through this large cyst. (C) DSH, 8 years old: large cysts, which transilluminate poorly, were present in both eyes. (D) DSH, 7 years old: a diffuse cortical cataract and large cysts are present. (E,F) Subgross and low magnification photomicrographs showing pigmented epithelial cysts attached to the posterior epithelium of the feline iris (arrows). This is often a feature of the traumatized feline eye.

  - Cysts can make contact with the lens, resulting in focal capsular opacity, and may even initiate posterior synechiae
  - Cysts can adhere to the endothelial surface of the cornea, and if they rupture or collapse, may be a source for endothelial pigmentation or atrophy
  - The presence of multiple uveal cysts in the posterior chamber can lead to collapse of the ciliary cleft and anterior displacement of the iris with closure of the irido-corneal angle, but secondary glaucoma is not common.
- Pars plana cysts in cats and horses (Fig. 9.9)
  - Cystic hyperplasia of the non-pigmented epithelium of the pars plana is a common finding in aged cats
  - The cysts are filled with Alcian blue-staining hyaluronic acid, which is digested by treatment with hyaluronidase
  - These cysts have no known clinical significance
  - Cysts of the pars plana epithelium also occur in aged horses (see Ch. 11)
- Multiple irido-ciliary cysts in Golden Retriever dogs, 'pigmentary uveitis' (Figs 9.10, 9.11)
  - The occurrence of multiple, thin-walled, irido-ciliary cysts is an important cause of glaucoma in Golden Retrievers. Within the COPLOW collection, there are 134 cases, representing 20% of glaucomas diagnosed in Golden Retrievers
  - Based entirely on submissions to the COPLOW collection, this condition was most prevalent in the Golden Retriever population in the North-eastern United States in the 1990s, which may reflect the common ancestry of this population
  - The condition is seldom diagnosed in Golden Retrievers in Europe, although a very similar condition has been reported in Great Danes. There is one case in a Great Dane in the COPLOW collection, and occasional cases with similar morphology in other breeds have been diagnosed at COPLOW
  - There are significant differences between the clinical presenting features and the histopathological features of this disease:

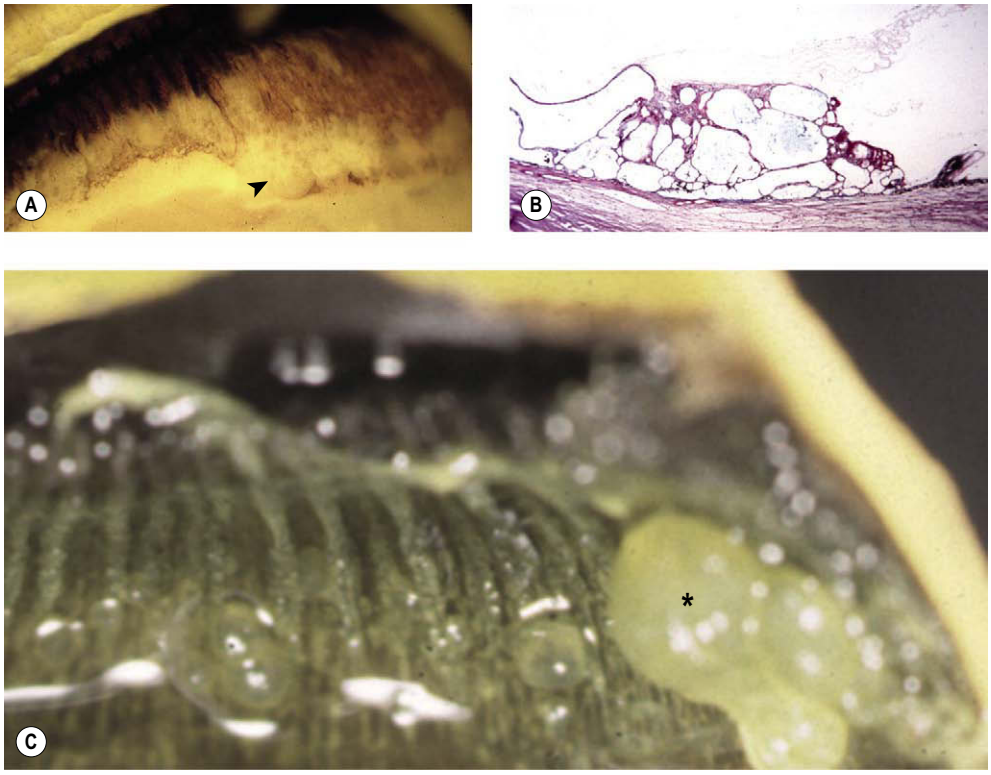


Figure 9.9 Pars plana cysts feline and equine. (A) Gross photograph showing cysts on the pars plana of the ciliary body in an aged feline eye (arrow). (B) Photomicrograph showing ciliary epithelial cysts filled with Alcian blue positive material (hyaluronic acid) (Alcian blue PAS). (C) Gross photograph showing a cluster of pars plana cysts (*) in an aged horse.

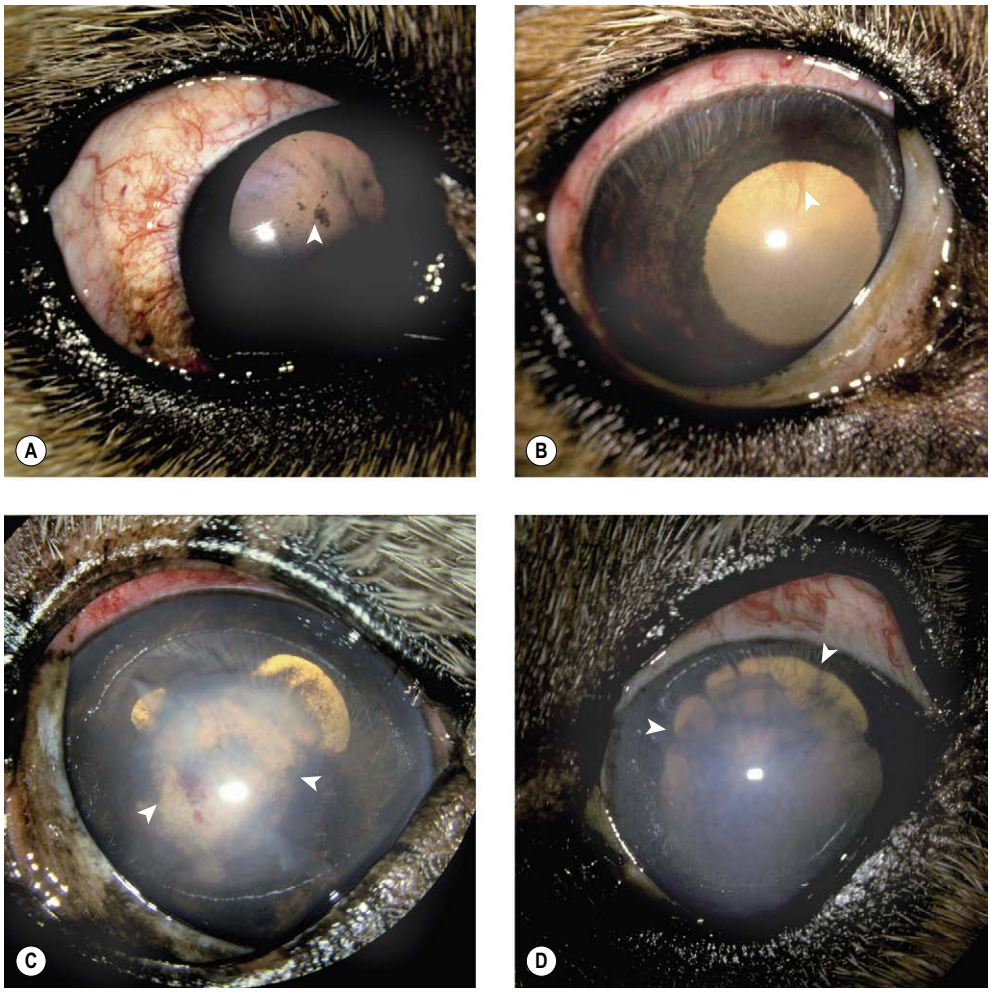


Figure 9.10 Golden Retriever thin-walled cysts (pigmentary uveitis), clinical. (A) Golden Retriever, 7 years old: the irides were both hyperpigmented. Focal areas of anterior capsule pigmentation (arrow) are present. Iris cysts could not be visualized on ocular examination. (B) Golden Retriever, 5.5 years old: pigment swirls are present (arrow) primarily at the equatorial lens. (C) Golden Retriever, 11 years old: posterior synechia resulted in an irregular pupil. A large white proteinaceous mass (between arrows) is present in the anterior chamber. (D) Golden Retriever, 10 years old: strands of posterior synechia (arrows) are present. Corneal edema and an anterior chamber proteinaceous mass contributed to the axial opacity.

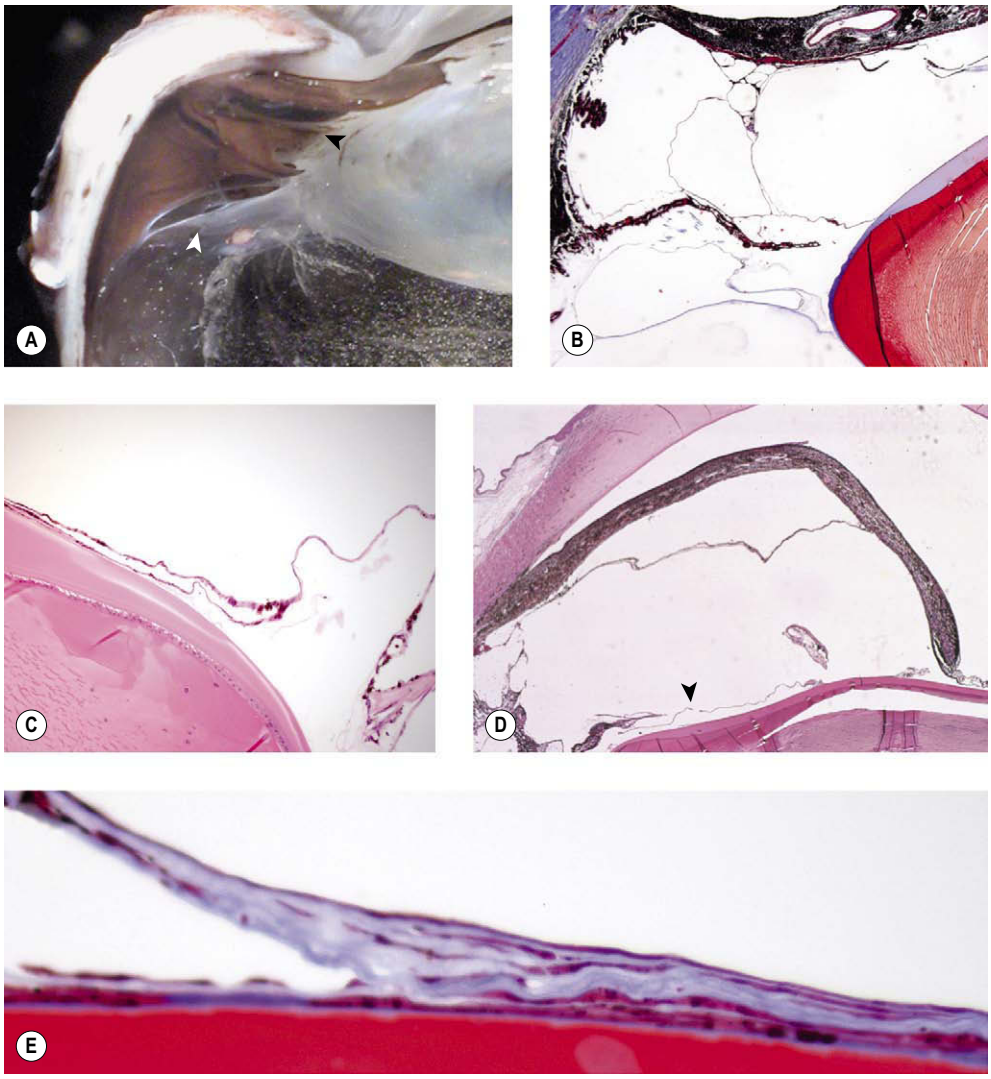


Figure 9.11 Golden Retriever thin-walled cysts (pigmentary uveitis), pathology. (A) Gross photograph showing the iris, posterior chamber, and remnants of thin-walled cystic structures stretched between the pars plicatus and the lens equator (white arrow). Posterior synechia and pigmented fragments of cysts adhere to the lens (black arrow). (B) Photomicrograph showing epithelial membranes and cyst walls crossing the posterior chamber and adherent to the anterior vitreous face. (C) Partially pigmented thin epithelial membrane is adherent to the lens capsule. (D) Iris bombe in an affected Golden Retriever. Notice the pigmented epithelial membrane (arrow) broadly adherent to the lens capsule. (E) Higher magnification photomicrograph showing thin epithelial cells and a small amount of blue collagen matrix adherent to the lens capsule (trichrome stain).

- Clinically, the disease presents as uveitis with aqueous flare, and proteinaceous and cellular debris and pigment recognized in the anterior chamber. Typically there is also pigment adherent to the lens capsule, often in a radial pattern, and to the posterior cornea, hence the clinical term 'pigmentary uveitis'. The condition often affects both eyes, although disease involvement is not generally symmetrical
- Histologically, the main defining characteristic of this disease is the presence of thin-walled epithelial cysts filling the posterior chamber and draped against the lens capsule and anterior face of the vitreous body. Inflammation is variable, and not consistently seen
- Affected globes are often heavily pigmented and free melanin pigment in the irido-corneal angle might play an important role in the pathogenesis of inflammation or glaucoma. Reduction in aqueous outflow by viscous material liberated from ruptured cysts, or simply anterior displacement of the iris by multiple cysts in the posterior chamber, could also contribute to the development of secondary glaucoma in affected dogs
- It should be acknowledged that, in a pathology collection, only severely affected globes, often with secondary glaucoma, are available for histopathological evaluation

■ Morphologic features of multiple irido-ciliary cysts in Golden Retrievers
- Thin-walled epithelial cysts, that may be either pigmented or non-pigmented, extending across the posterior chamber
  - Cyst epithelium is thin, almost squamous in appearance
  - A PAS stain often reveals a magenta-staining basal lamina along with the epithelial cells
  - A cell-poor collagenous matrix may also be identified, adjacent to the cyst epithelium or attached to the lens capsule
- Cyst walls or portions of cyst walls are adherent to the anterior face of the vitreous body or the equatorial lens capsule
  - When present on the lens capsule, the cyst epithelium often extends anteriorly, towards the anterior pole of the lens. These pigmented thin epithelial fragments are probably what is recognized as pigment adherent to the lens clinically
- Posterior synechiae or iris bombé are frequently seen in globes removed because of secondary glaucoma

  - Preiridal fibrovascular membranes are commonly encountered, often with concurrent peripheral anterior synechiae
  - Focal retro-corneal membranes are often seen, frequently with pigment entrapment
    - Fragments of thin-walled cysts are seldom, if ever, recognized in the anterior chamber
  - Intraocular hemorrhage is often seen
  - Free pigment in the irido-corneal angle may play a role in the development of glaucoma, just as it might in glaucoma associated with goniodysgenesis.
- Multiple irido-ciliary cysts are a characteristic finding in Rocky Mountain horses with an inherited complex of congenital ocular anomalies (see Ch. 3)
  - The cysts are thin-walled and translucent and are generally present in both eyes of affected horses.

Comparative Comments

The major congenital and developmental abnormalities of the human uveal tract are colobomas, aniridia, persistent pupillary membrane, persistence of the tunica vasculosa lentis, and iris cysts.

Neovascular proliferation and tissue fibrosis in the uvea (Fig. 9.12)

Neovascular proliferation

The uvea is prone to neovascular proliferation and tissue fibrosis in circumstances which favor local production of cytokines, most prominently vascular endothelial growth factor (VEGF)

- Conditions that are commonly associated with uveal neovascular membranes in domestic animals include:
  - Uveitis
  - Trauma, including intraocular surgery
  - Intraocular neoplasia
  - Retinal detachment and associated retinal hypoxia
  - Other causes of ocular or retinal hypoxia or ischemia, including glaucoma
- Common sites of uveal neovascular membrane formation are:
  - Pre-iridal fibrovascular membrane (PIFVM), which is most commonly recognized on histopathology
    - Since there is no epithelial lining to the anterior iris surface, the new vessels and fibroblasts that constitute the fibrovascular membrane do not have to penetrate an epithelium, as would be required at other sites of fibrovascular proliferation within the eye
    - PIFVM is seldom mentioned as a clinical finding on pathology submission forms
      - In dogs, however, careful slit-lamp biomicroscopic examination by an experienced observer may be required to identify PIFVM, which is much more difficult to appreciate clinically against the darker background of the typical, brown canine iris
      - Clinicians may recognize the effects of PIFVM, rather than directly identifying the membrane itself, e.g. by identifying ectropion or entropion uveae, whereby the pupillary zone of the iris is distorted by the contractile effects of a PIFVM
  - Posterior iridal fibrovascular membrane
  - Cyclitic membrane
    - Fibrovascular tissue penetrates the ciliary epithelium and extends across the anterior vitreous face, incorporating the ciliary processes. Advanced cases can span the globe across the anterior vitreous and extend behind the lens
  - Intravitreal membranes, extending from the pars plana into the body of the vitreous. Intravitreal membranes are generally associated with intraocular hemorrhage
  - Intravitreal, or epiretinal membranes extending from the optic nerve head into the body of the vitreous and on the inner surface of the retina are infrequently recognized in domestic animals
- In contrast to the human eye, the eyes of domestic animals seldom develop proliferative membranes directly on the retinal surface, (proliferative vitreoretinopathy or epiretinal membranes)
- It is appropriate here to re-emphasize that the chambers of the eye, the anterior and posterior chamber and the vitreous body, are not luminal spaces. Rather, they are modified, cell-poor, extracellular spaces. As such, it comes as no surprise that they are easily invaded by fibrovascular membranes.

Fibrovascular proliferation

Fibrovascular proliferation (granulation tissue formation) is almost never seen *within* the uveal tissue proper.

- It can therefore be assumed that there is some inhibitory process at work within the uveal tissues, preventing the formation of harmful scar tissue directly within the uveal stroma.

Clinically significant complications of fibrovascular proliferation

- Intraocular hemorrhage
- Synechiae
  - Peripheral anterior synechiae
  - Posterior synechiae
- Traction within the vitreous leading to retinal detachment
- Glaucoma.

Neoplastic membranes

Neoplastic membranes on the anterior surface of the iris are a prominent feature in metastatic neoplasia. See later in this chapter for further discussion of metastatic neoplasia involving the uvea.

Comparative Comments

In the human, one of the most important and intensely studied examples of neovascular proliferation is in the wet or exudative type of age-related macular degeneration. These eyes have fibrovascular tissue present between the inner and outer layers of Bruch's membrane, beneath the retinal pigment epithelium or in the subretinal space. This leads to fluid leakage giving rise to serous retinal detachments, and vessel rupture, resulting in subretinal and intraretinal hemorrhages.

Inflammation-uveitis

Clinical and pathologic diagnoses

Distinct and separate criteria are used by the clinician and by the pathologist in the diagnosis of uveitis. Thus, in some cases, it can be difficult to reconcile clinical and pathologic diagnoses.

- The clinical diagnosis of uveitis relies heavily on the manifestation of aqueous flare, an indication of protein

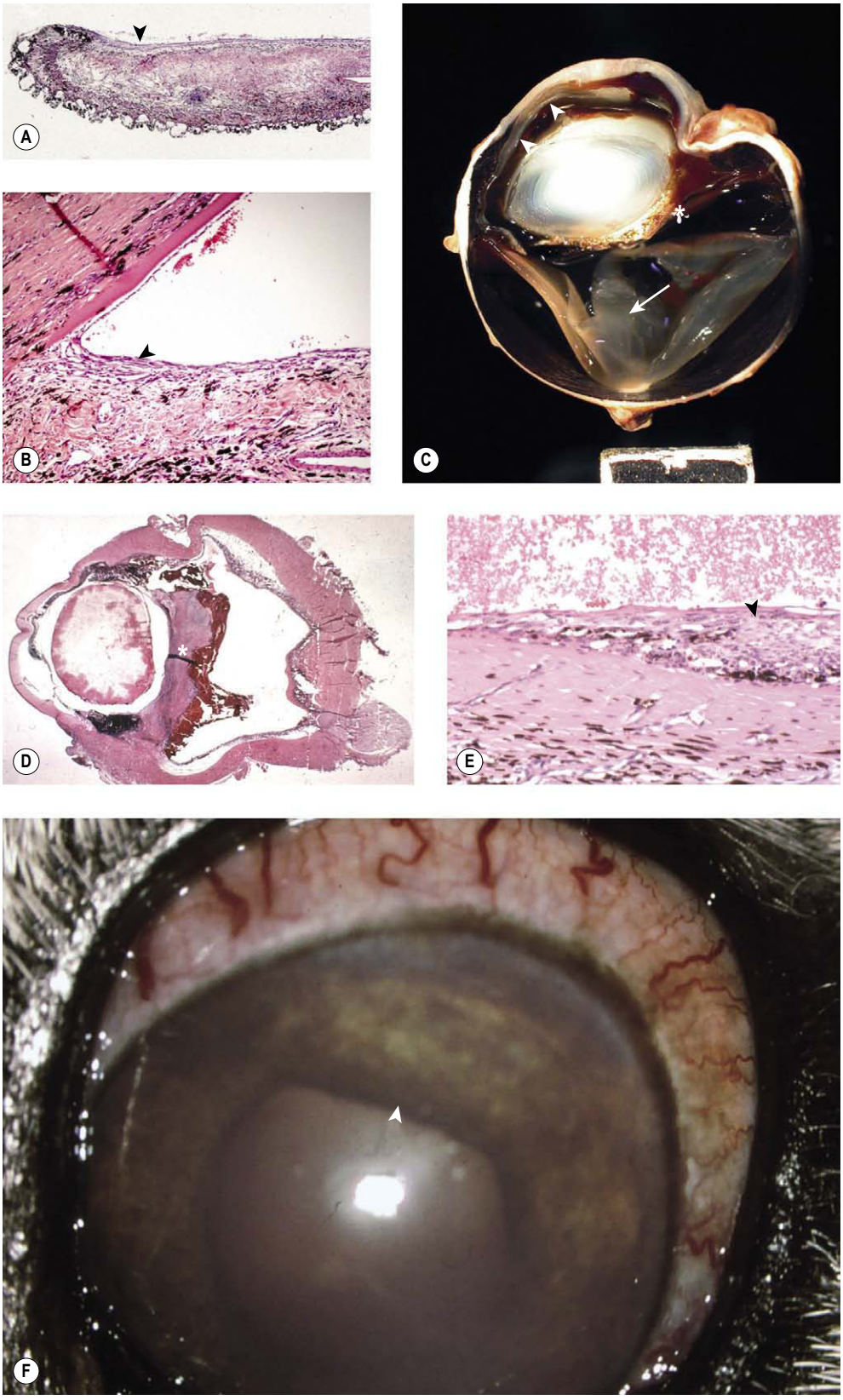


Figure 9.12 Fibrovascular membrane proliferation. (A) Low magnification photomicrograph of a canine iris showing a preiridal fibrovascular membrane (arrow) and ectropion uveae on the anterior surface. (B) Photomicrograph showing preiridal fibrovascular membrane (arrow) and peripheral anterior synechia in a dog. A circumferentially affected globe would likely have neovascular glaucoma. (C) Gross photograph of a canine globe showing a preiridal fibrovascular membrane (arrowheads), cyclitic membrane (*), and an early fibrovascular membrane extending into the vitreous from the optic nervehead (arrow). (D) Subgross photomicrograph of a dog eye showing an extensive cyclitic membrane (*). (E) Photomicrograph of a dog eye showing a choroidal fibrovascular proliferation (arrow). (F) Siberian Husky, 10 years old: detail of iris architecture is lost. No tapetal reflex can be seen. Posterior synechia (arrow) resulted in a secondary glaucoma.

or cells in the aqueous humor. Protein in the aqueous humor is very difficult for the histopathologist to demonstrate
- The histopathologic diagnosis of uveitis relies on the demonstration of cellular hallmarks of inflammation directly within the uveal stroma. There is no reliable way to make this determination clinically.

Feline lympho-plasmacytic uveitis (L-P uveitis) (Fig. 9.13)

There are 558 cases of feline lympho-plasmacytic uveitis in the COPLOW collection, 11% of feline submissions.

- Lympho-plasmacytic uveitis is one of the most common causes of feline glaucoma and, in the COPLOW collection, is second only to diffuse iris melanoma as the most common cause of feline glaucoma resulting in enucleation
  - Although L-P uveitis in cats is not always clinically associated with glaucoma, globes with concurrent glaucoma are overwhelmingly more likely to be submitted to COPLOW for histopathologic evaluation
- Although much studied, the etiopathogenesis of L-P uveitis in cats has not yet been elucidated, with many cases being termed idiopathic
  - Lympho-plasmacytic inflammation is also commonly seen in traumatized eyes, suggesting that L-P uveitis is a non-specific

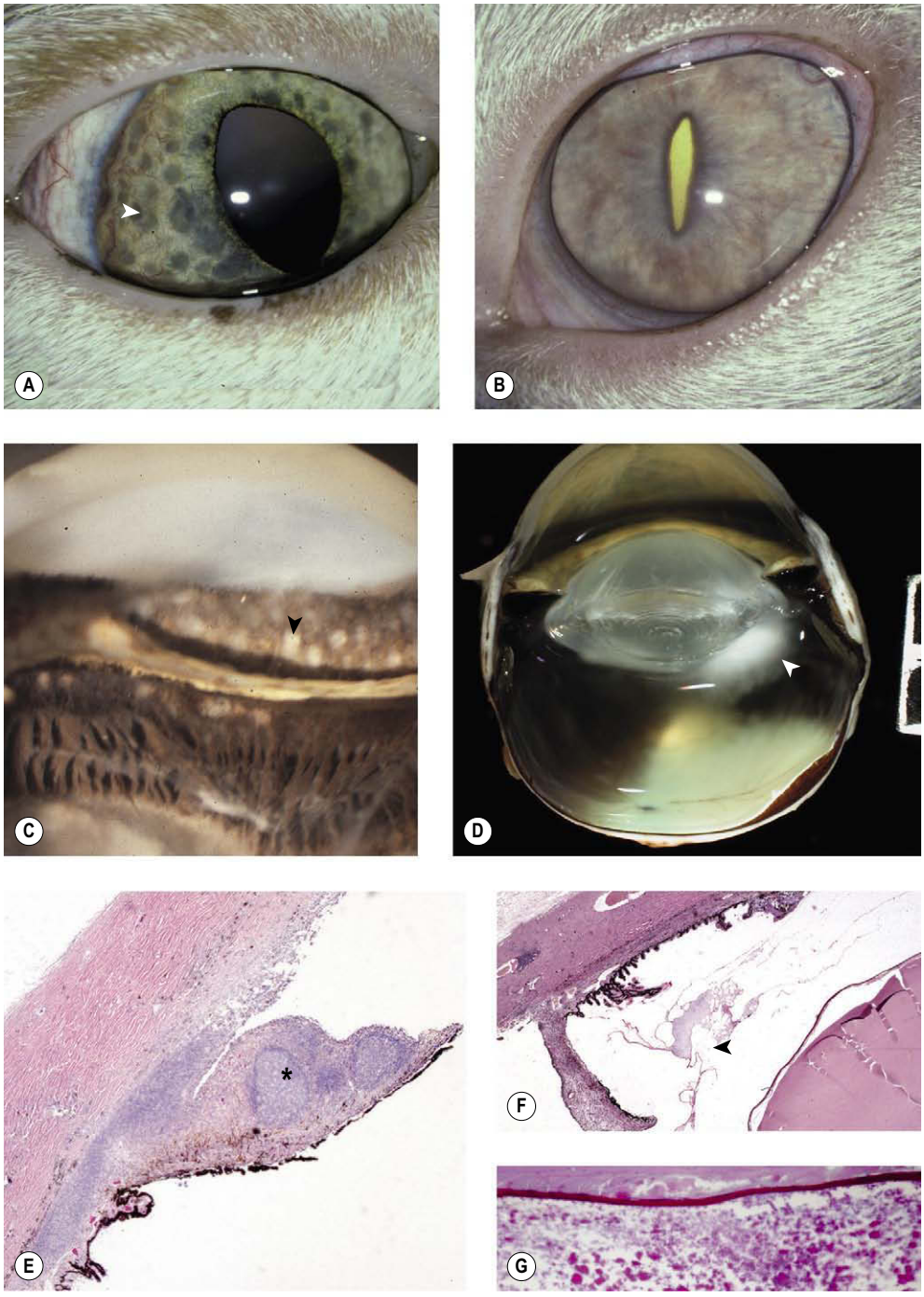


Figure 9.13 Feline lymphoplasmacytic anterior uveitis. (A) DSH, 6 years old: multiple Busacca nodules (arrow) are present over the entire iris. Toxoplasmosis was the presumed etiology based on serology. (B) Siamese, 6 months old: the iris is severely swollen. A severe aqueous flare and miosis are also present. *Bartonella* was the presumed etiology based on serology. (C) Gross photograph showing the anterior uvea of a cat with lymphoplasmacytic uveitis. Multiple lymphoid nodules appear as raised tan round foci (arrow). There is also considerable recession of the irido-corneal angle. (D) Gross photograph of an affected cat eye showing a localized flare in the vitreous adjacent to the posterior lens capsule (arrow) typical of the release of lens protein. When the flare is seen, it is not known whether the lens protein contributes to or is the cause of uveitis. (E) Photomicrograph of the iris from an affected cat showing intense inflammatory infiltration with lymphocytes and plasma cells, including the formation of lymphoid follicles (*). (F) Low magnification photomicrograph showing condensed vitreous in the posterior chamber (arrow) of an affected cat. (G) Photomicrograph of the posterior pole of the lens and vitreous showing the typical granular appearance of the released lens protein material, similar to that shown in (D).

feline ocular immune response that may be initiated by multiple causes
  - Based on serologic studies, *Toxoplasmosis* and *Bartonellosis* have been cited as potential etiologic agents
- Morphologic features of L-P uveitis in cats include:
  - Lymphocytes and plasma cells in the anterior uvea
    - The ratio of lymphocytes to plasma cells can vary dramatically between cases
    - The absolute numbers of inflammatory cells can also vary dramatically between cases, and is important, neither to the diagnosis of L-P uveitis, nor to the subsequent development of secondary glaucoma
  - Formation of lymphoid follicles in the iris stroma or the anterior ciliary body stroma
    - Although not all cases demonstrate lymphoid follicles, these are a feature that is not commonly seen in response to chronic uveitis in other species, except horses
  - Lymphocytic cells within the non-pigmented epithelium of the ciliary body
  - Many cases have lens luxation or subluxation
    - This morphologic feature needs to be assessed at the time of globe trimming
  - Many cases demonstrate vitreous liquefaction
    - This morphologic feature also needs to be assessed at the time of globe trimming
    - Whereas the bulk of the vitreous body may be liquid, the anterior vitreous face often appears abnormally dense or condensed
  - Changes in the anterior vitreous:
    - it is important to use an Alcian blue-PAS stain to evaluate the anterior vitreous
    - The anterior face of the vitreous often contains an excess of spindle cells and collagen
    - The anterior vitreous is often displaced into the posterior chamber or through the pupil, into the anterior chamber
    - Granular hypereosinophilic protein may be observed in the anterior vitreous, adjacent to the posterior lens capsule
      - Although it is not always possible to demonstrate a break in the thin, posterior lens capsule, this abnormality of the anterior vitreous that is suggestive of lens protein leakage is seen relatively frequently. In these cases, the inflammation observed may represent a lens-induced uveitis
- Mechanisms of secondary glaucoma in L-P uveitis
  - Many assume that secondary glaucoma is related to obliteration or occlusion of the drainage angle structures by inflammation or attendant pre-iridal fibrovascular membranes, however, lens luxation and/or anterior vitreous prolapse may also be implicated in some cases.

Equine recurrent uveitis (ERU), periodic ophthalmia, moon blindness (Figs 9.14, 9.15)

There are 78 cases of equine recurrent uveitis in the COPLOW collection, 20 of them in Appaloosa horses.

- ERU is the most common cause of cataract, glaucoma, phthisis bulbi and blindness in horses
- There is a breed predilection for the Appaloosa
- It is important to be aware that not all cases of uveitis in horses are attributable to ERU
- The clinical syndrome is characterized by recurrent bouts of inflammatory disease leading to progressive ocular degeneration. In some horses the disease has an insidious onset, with minimal clinical signs noted until significant secondary complications, such as cataract, glaucoma and/or phthisis bulbi become apparent
- The etiopathogenesis of ERU has not been definitively established and many causes have been postulated. However, current evidence implicates Leptospiral ocular infection and auto-immunity as the important factors in the pathogenesis ERU
  - Evidence to support the role of Leptospirosis in the pathogenesis of ERU includes:
    - Inoculation of susceptible ponies with *Leptospira interrogans* serovar *pomona* causes a syndrome of recurrent uveitis that is clinically and histopathologically indistinguishable from ERU
    - Some affected horses have elevated antibody titers and the titers are even higher in the aqueous
    - *Leptospira* serovars have been detected by culture and/or PCR in vitreous and aqueous, and even fixed ocular tissues of affected horses. However, this has been a very inconsistent finding in ERU cases in North America compared with ERU cases from continental Europe
    - While Leptospirosis may induce uveitis in horses, the recurrent nature of inflammation in ERU most-likely reflects the role of auto-immunity in its pathogenesis
  - Evidence that supports a role for auto-immunity in the pathogenesis of ERU includes:
    - During the active phase of the disease, there are circulating or local antibodies to various ocular proteins
    - Leptospira organisms are not consistently detected in ocular fluids and tissues of all affected horses
    - Immunopathologic studies support the 'auto-aggressive' nature of the disease, demonstrating a preponderance of CD4+ T-cells and increased transcription of IL-2 and IFN-γ with low IL-4, that are characteristic of a Th1-like inflammatory response
    - A role for retinal auto-antigens, including inter-photoreceptor binding protein, cellular retinaldehyde binding protein, recoverin and retinal-S antigen (arrestin), has been demonstrated in experimental models and spontaneous ERU
    - Immunogenetic investigations have suggested an association between ERU susceptibility and certain equine lymphocyte antigen (ELA) haplotypes
    - Some affected horses develop a subclinical lymphocytic inflammation in the pineal gland which shares many antigens with the retina
- Distinctive morphologic features of ERU include:
  - Lympho-plasmacytic uveitis, with lymphoid follicle formation in some cases. Equine recurrent uveitis and feline L-P uveitis are the two diseases in which this feature is prominent. Lymphoid follicles are otherwise a rare finding in the uveal tract
  - Lymphocytes and/ or plasma cells within the non-pigmented ciliary epithelium
  - Hypereosinophilic linear inclusions in the cytoplasm of non-pigmented ciliary body epithelial cells
    - Masson's trichrome stain facilitates the identification of these bright red-staining, intra-cytoplasmic inclusions
    - By electron microscopy these inclusions represent crystalline arrays of protein. At the margins of the inclusions, fragments of a double membrane are seen suggesting that the inclusions develop within mitochondria, breaking through the membrane
  - Deposition of a cell-poor hyaline protein on the inner surface of the non-pigmented ciliary body epithelium

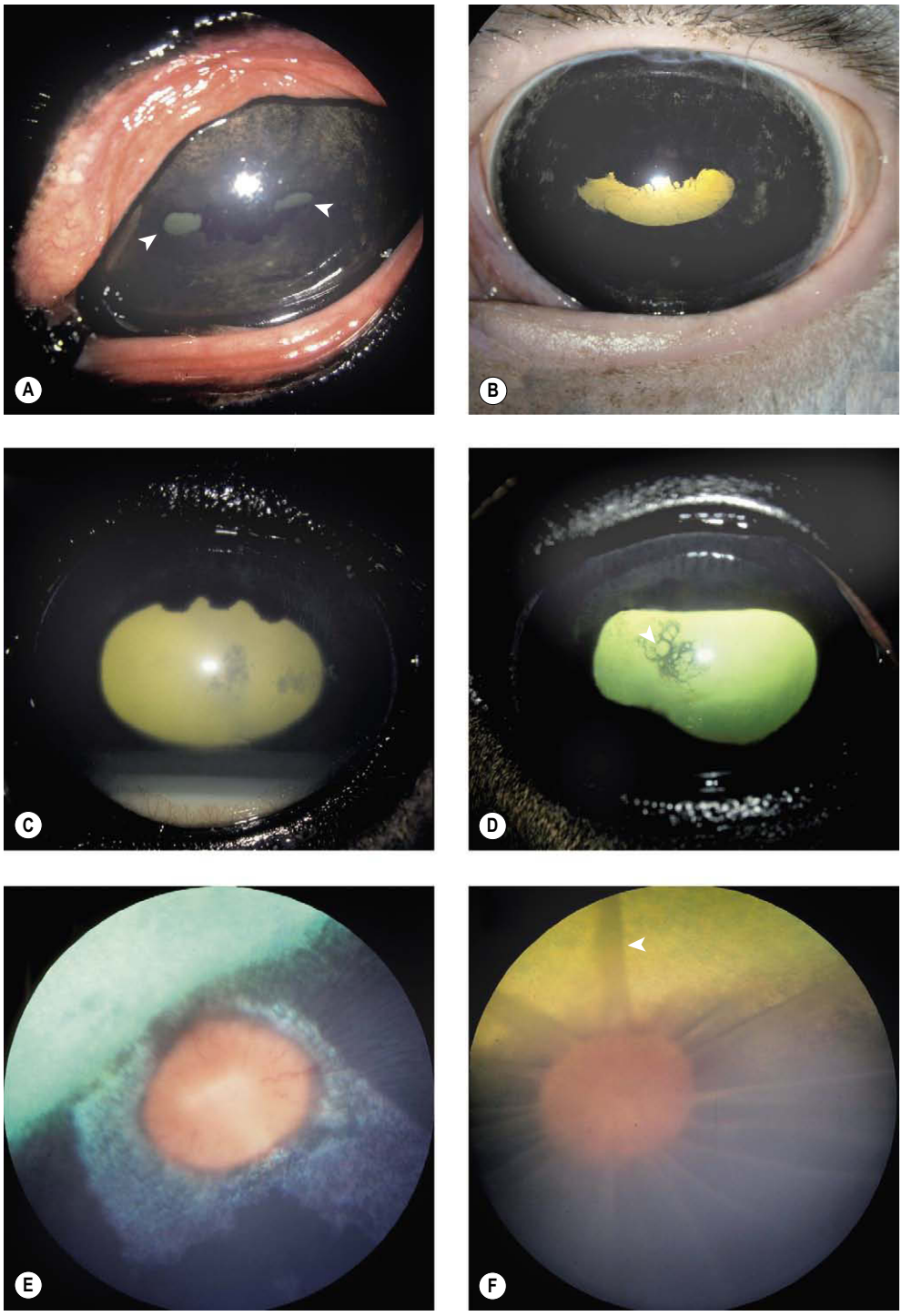


Figure 9.14 Equine recurrent uveitis, clinical. (A) American Saddlebred Horse, 7 years old: severe miosis and posterior synechia resulted in only two small areas of visible pupil (arrows). (B) Appaloosa, 10 years old: chronic uveitis resulted in an irregular pupil margin and a yellow discoloration of the vitreous. (C) Thoroughbred, 6 years old: in addition to the aqueous flare, hypopyon is present inferiorly. (D) Thoroughbred, 10 years old: aqueous flare, dyscoria, and an anterior cortical cataract (arrow) are present in this case. (E) Thoroughbred, 6 years old: peripapillary chorioretinopathy, called a 'butterfly' lesion, and anterior uveitis are present in this eye. (F) American Standardbred, 4 years old: hyalitis, optic neuritis, and radiating retinal detachment (arrow), termed a sunburst detachment, are present.

  - Stains positive with Congo red stain, a feature of amyloid
  - Shows green birefringence when viewed with intense polarized light, which is also a feature of amyloid
  - Stains blue with Masson's trichrome, which is typical of collagen
  - Filaments have ultrastructural characteristics suggestive of collagen

- Other morphologic features of ERU, which are common findings but not necessarily specific, include:
  - Cataract
  - Retrocorneal membranes and corneal wrinkling
  - Anterior and/or posterior synechiae
  - Fibrovascular membranes
  - Retinal detachment and/or retinal degeneration
  - Optic nerve inflammation, degeneration and gliosis

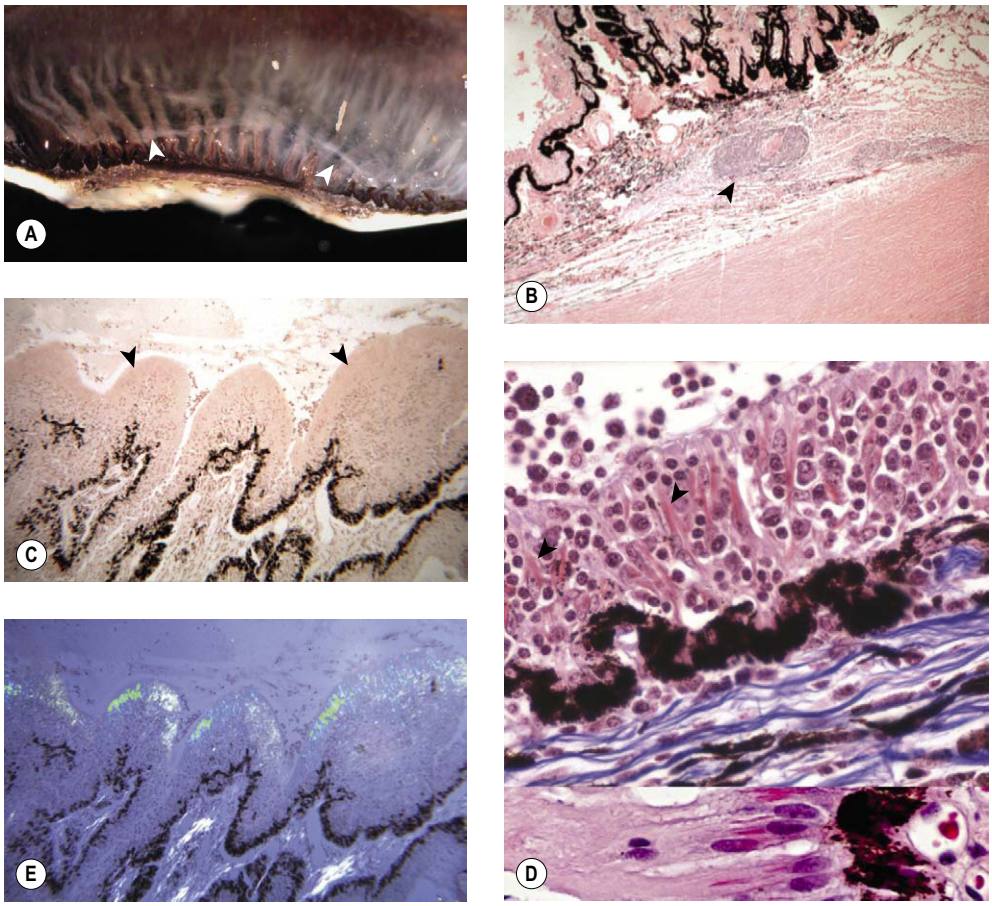


Figure 9.15 Equine recurrent uveitis, pathology. (A) Gross photograph of equine eye showing an inflammatory membrane tightly adherent to the inner aspect of the ciliary body (arrows) in equine recurrent uveitis (ERU). (B) Photomicrograph of an affected horse showing a lymphoplasmacytic infiltrate in the ciliary body stroma including a lymphoid follicle (arrow), a feature highly suggestive of ERU. (C) A photomicrograph of the pars plicata of the ciliary body of an affected horse showing a membrane of cell-poor amyloid-like protein (arrows). (D) Photomicrograph of the ciliary body epithelium showing numerous inflammatory cells within the epithelium and hypereosinophilic linear inclusions in the cytoplasm of the affected cells (small arrows). The lower inset shows these bodies at a higher magnification. (E) Photomicrograph showing green birefringence of a Congo red-stained section of the ciliary body of an affected horse. The birefringent membrane is the same one illustrated in (C).

- It appears that significant posterior uveitis, characterized by pronounced chorioretinal disease and vitreous opacification, is less frequently observed in the USA than in Europe
  - This may reflect differences in the ability to establish persistent intraocular infections between the predominant *Leptospira* isolates from ocular fluids of horses with ERU in Europe (*L. kirschneri serovar Grippotyphosa*, strain Duyster) and North America (*L. interrogans serovar Pomona*).

Canine uveodermatologic syndrome, Vogt–Koyanagi–Harada-like syndrome (VKH) (Figs 9.16–9.18)

There are 83 cases of uveodermatologic syndrome in the COPLOW collection, 23 of which are in Akitas.

- This canine uveo-dermatologic syndrome is considered a model for human Vogt–Koyanagi–Harada syndrome
- The Akita breed is predisposed to uveodermatologic syndrome
- The human disease generally affects dark-skinned people between 20 and 50 years old and is most common in Japan. The bilateral uveitis is accompanied by pigment loss in the skin and/or hair. The human disease is strongly related to certain HLA tissue types
  - Increased frequency of certain DLA class alleles has been identified in Akitas in the USA, and these alleles carry a higher relative risk for uveodermatologic syndrome
- Canine uveodermatologic syndrome and human VKH are both thought to be an autoimmune disease that targets melanin or a component protein expressed in melanocytes. Tyrosinase, or tyrosinase-related proteins are considered to represent strong candidates as the target antigen. Peptides from tyrosinase related protein-1 have been used to induce experimental uveodermatologic syndrome in Akitas
- Clinically the syndrome is characterized by uveitis that is generally bilaterally symmetrical and unilateral disease is rare. Retinal detachment and glaucoma are seen in many cases
  - A case report describing a dog with unilateral disease provides an interesting insight into the pathogenesis. This dog had asymmetric uveal pigment dilution *(heterochromia irides)*, the blue eye being spared the panuveitis recognized in the brown eye
- Poliosis, vitiligo and alopecia are frequently recognized, with depigmentation that may be localized to the facial region, particularly to the nasal planum and lips, or may be generalized
- Morphologic features of canine uveodermatologic syndrome include:
  - The hallmark feature of uveodermatologic syndrome is granulomatous uveitis
    - Uveal inflammation is always histiocyte-rich
      - Some dogs have marked uveal thickening because of solid sheets of histiocytic inflammation, whereas others have no thickening and a very bland histiocytic infiltrate
      - Histiocytes are peppered with melanin granules
      - Inflammation can be more severe in any part of the uvea but the choroid is always affected

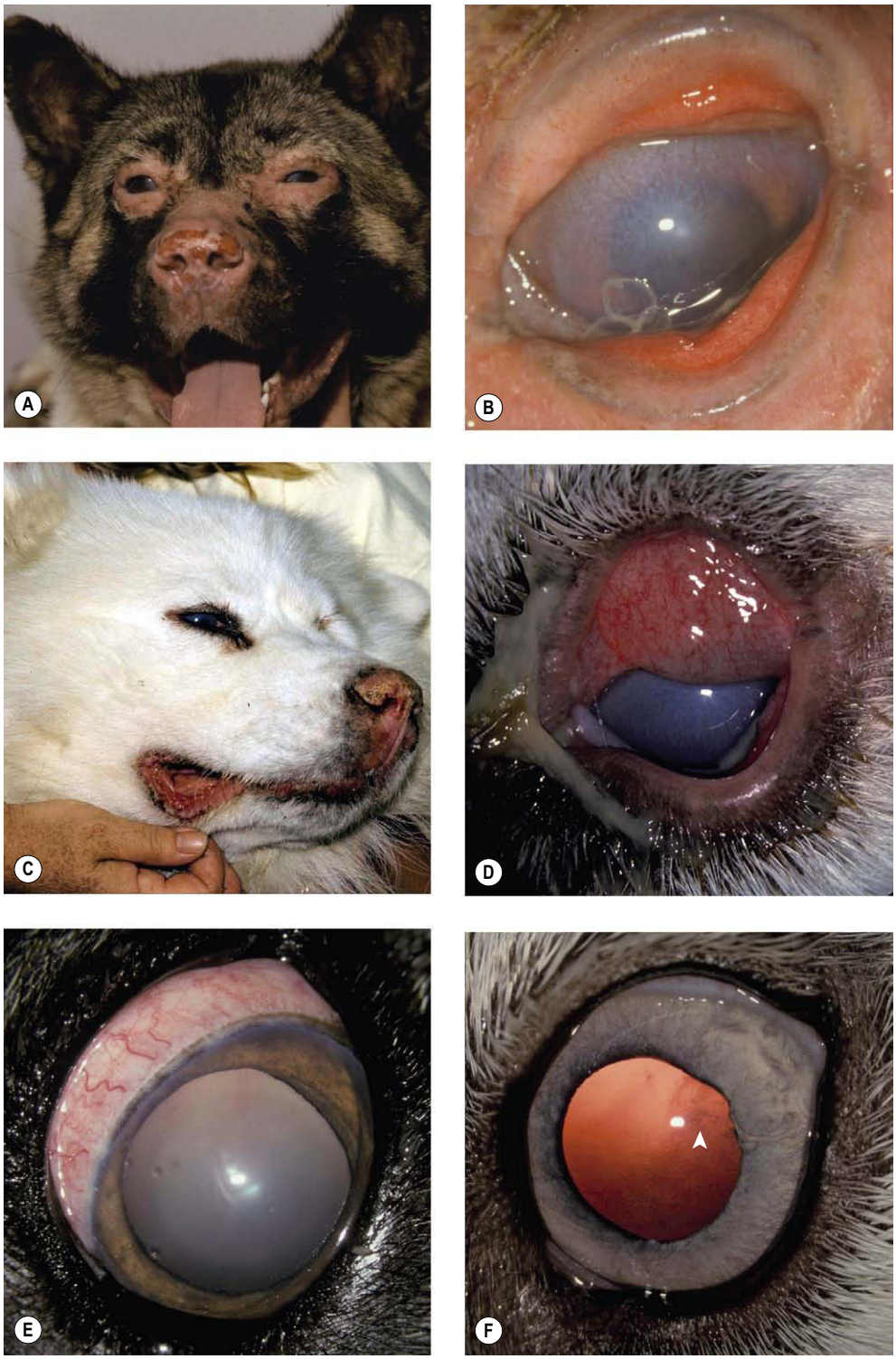


Figure 9.16 Canine uveodermatologic syndrome (VKH-like), clinical. (A) Japanese Akita, 10 months old: periocular, nasal and labial depigmentation is present. (B) The left eye of the dog in (A) showing corneal edema and vascularization. A poorly dilated pupil is also present. (C) Samoyed, 14 months old: severe erosion and depigmentation are seen at the labium and nasal planum. (D) The left eye of the dog in (C) showing severe corneal edema and chemosis. (E) Japanese Akita, 3 years old: limbal edema and a swollen iris are present. (F) Siberian Husky, 18 months old: dyscoria and engorged iris vessels are present. Pigment is visible on the anterior lens (arrow).

    - The distribution of the inflammation is highly variable but, if both eyes are available for examination, the symmetry in distribution between eyes is striking
- There is a mismatch between the degree of granulomatous inflammation observed in the uvea, and the relatively 'quiet' appearance of the vitreous, aqueous, retina, and cornea
- Granulomatous inflammation centered on pigmented cells is a defining feature of canine uveodermatologic syndrome
    - Clusters of histiocytes within the choroid and subtending the pigmented retinal pigment epithelium (RPE) in a manner reminiscent of Dalen-Fuchs nodules. In humans, these collections of epithelioid cells between the RPE and Bruch's membrane are associated with

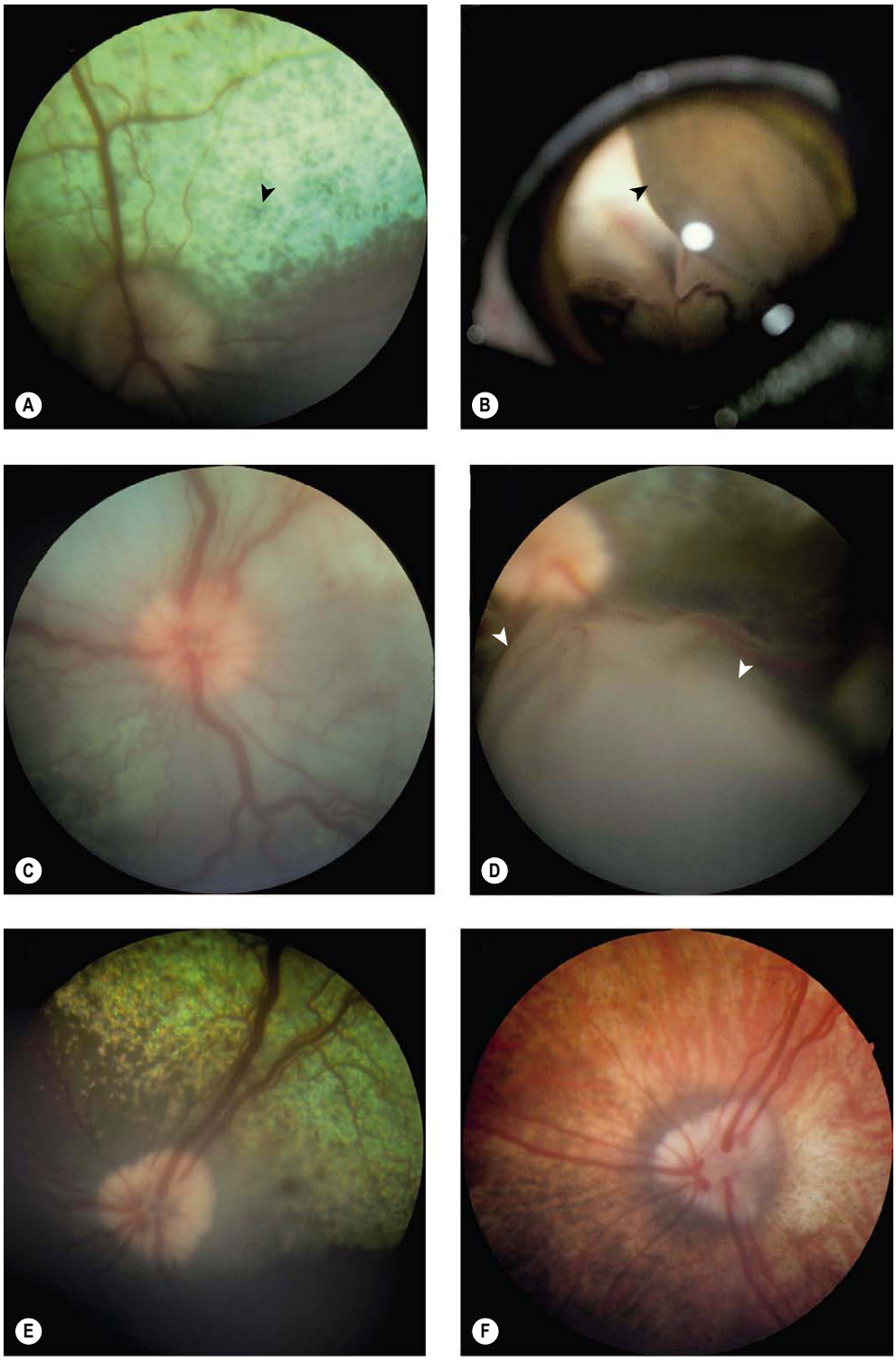


Figure 9.17 Canine uveodermatologic syndrome (VKH-like), fundus. (A) Japanese Akita, 6.5 years old: optic neuritis is present in this blind dog. The arrow points to one of the many areas of abnormal pigmentation in the tapetal retina. (B) Japanese Akita, 3 years old: the optic disc is poorly visualized. The arrow points to the edge of a large bullous detachment. (C) Samoyed, 8 months old: retinal vessels are dilated. The optic disc is swollen and the entire retina is edematous and elevated. (D) Japanese Akita, 7 years old: the arrows delineate a large bullous retinal detachment. (E) Samoyed, 2 years old: a swollen optic disc, dilated retinal vessels, and tapetal pigment changes are present. (F) Samoyed, 5 years old: the same eye as in (E), 3 years later, showing the loss of the tapetum and pigment in the retinal pigmented epithelium and choroid.

certain forms of granulomatous uveitis, including VKH and sympathetic ophthalmia
- In skin biopsies from affected dogs with de-pigmentation there will be histiocytic inflammation, with melanophage cells subtending the surface epithelium
- Inflammation of the meninges is common in the human disease but appears to be rare in dogs.

Canine asymmetric uveitis (Fig. 9.19)

- There are 79 cases of asymmetric uveitis in the COPLOW collection, 17 of which are in Poodles, however the records seldom report which Poodle type. Although this diagnosis is made fairly frequently in the COPLOW submissions, the condition has not been reported in the veterinary literature.

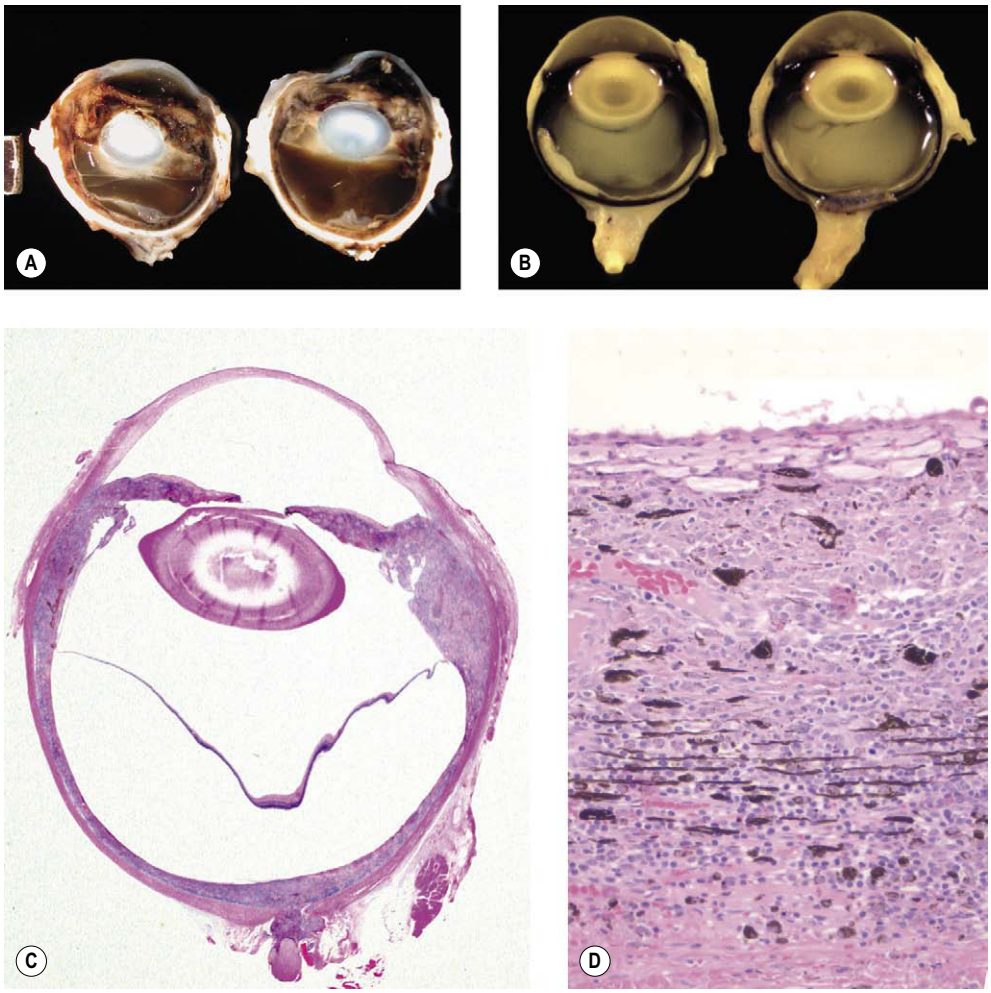


Figure 9.18 Canine uveodermatologic syndrome (VKH), pathology. (A,B) Gross photographs showing both globes from two dogs with canine uveodermatologic syndrome, illustrating the diffuse thickening of the affected uvea and the bilateral symmetry that is characteristic of the disease. The globes in (B) are fixed in Bouin's solution, which accounts for the yellow color. (C) Subgross photomicrograph of the globe from an affected dog showing diffuse uveal thickening due to a histiocytic inflammatory cell infiltrate. Retinal detachment is seen but the retina, vitreous and aqueous are relatively quiet. (D) Photomicrograph of the choroid from an affected dog showing a histiocyte-rich infiltrate, causing thickening of the choroid behind the tapetum.

- There are 52 females and 24 males among the cases with this diagnosis

- If the histopathological features of asymmetric uveitis are identified in an enucleated globe, then the remaining eye should be considered at risk of developing uveitis with similar morphologic features. Early and aggressive anti-inflammatory therapy may prevent severe ocular disease in the second eye
  - There are 23 cases in the COPLOW collection with confirmed disease in the second eye including 10 cases in which the second eye was submitted and had similar pathologic features to the original eye
  - The time between enucleation of the first eye and the clinical onset of disease in the second eye ranged from almost immediately to 4 years
- The diagnosis of asymmetric uveitis is dependent on recognition of a characteristic pattern of granulomatous uveitis with the following morphologic features:
  - Sheets of pyogranulomatous inflammatory cell infiltrate, forming a blanket-like covering on the inner surface of any part of the uveal tract or the inner retina. Rarely, this 'blanket' of inflammation extends across the posterior cornea
    - Histiocytic cells tend to line up perpendicular to the uveal surface
  - Inflammation within the retina and segmental retinal necrosis
- The same morphologic features will be seen in the second eye if it is submitted for evaluation, concurrently or subsequently
- Aside from the characteristic features which define asymmetric uveitis, in most instances the first affected globe shows other features suggesting a penetrating injury such as lens capsule rupture, scleral defect, sepsis in the globe or a foreign body. However, evidence of a penetrating injury is not always identified and a history of trauma is seldom reported by the submitting clinician. Careful scrutiny of serial sections may be required to identify such evidence of penetrating injury or episcleral inflammation
- Severe uveitis that develops in some dogs with diabetic cataract, with lens protein-associated, macrophage-rich endophthalmitis, presents a histological appearance that is very similar to asymmetric uveitis.

Lens-induced uveitis, phacolytic uveitis (Fig. 9.20)

There are 50 cases of lens-induced uveitis in the COPLOW collection. Because this phenomenon is commonly seen as part of a complex, multifaceted disease process, it is likely that the condition is significantly under-represented in our collection.

- Lens-induced uveitis almost invariably accompanies mature, intumescent or hypermature cataract. Induction of an inflammatory response within the uvea is thought to occur secondary to the leakage of lens proteins through an intact lens capsule, as part of a degenerative process that also results in lens shrinkage and capsule wrinkling

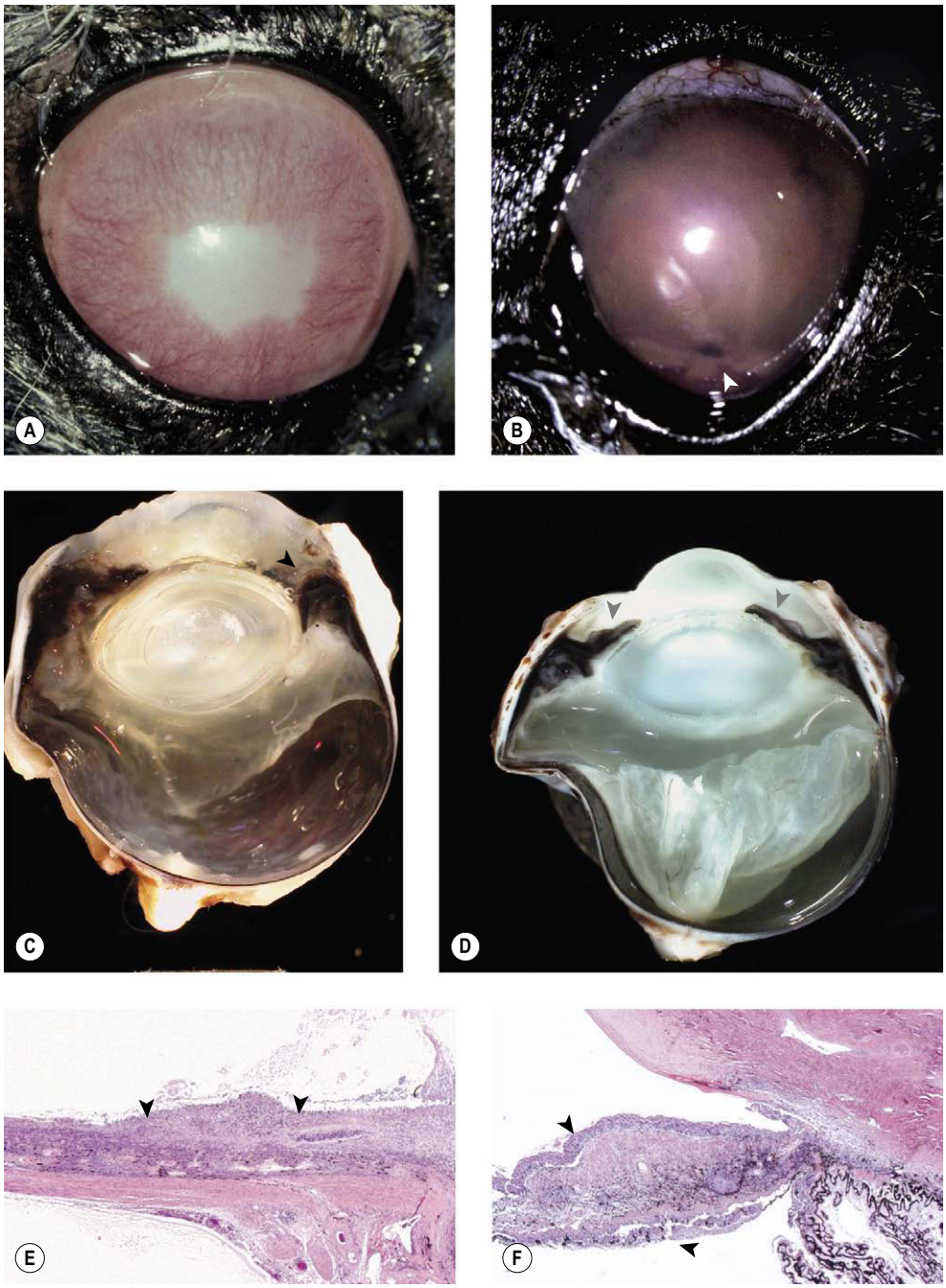


Figure 9.19 Canine asymmetric uveitis. (A) Poodle, 14 years old: chronic uveitis resulted in severe corneal edema and superficial corneal vascularization in the right eye. (B) This is the left eye, previously normal, of the dog in (A), 3 months later. The detail of the anterior segment is difficult to view due to the severe flare and fibrin. Hypopyon is present at the arrow. (C,D) Gross photographs of globes from two different dogs with asymmetric uveitis showing an inflammatory membrane lining the anterior uvea (arrows) and considerable exudates in the aqueous and vitreous and around the detached retina. (E) Photomicrograph of the choroid of an affected dog showing a macrophage-rich membrane carpeting the inner choroid and subretinal space (arrows). (F) Photomicrograph of the iris from an affected dog showing a macrophage-rich membrane carpeting the surface of the iris front and back (arrows).

- Morphologic features of lens-induced uveitis include:
  - Mild to moderate lympho-plasmacytic infiltrate in the anterior uveal stroma. This is a non-specific change and the diagnosis of lens-induced uveitis should only be made if the lens pathology is appropriate and there are no other changes identified that are consistent with a different pathogenesis
  - Globes removed and submitted for histopathology often have glaucoma associated with posterior synechiae, iris bombé, or pre-iridal fibrovascular membranes with extensive peripheral anterior synechiae
- Phacolytic uveitis in the special case of rapidly progressing, intumescent diabetic cataract and lens capsule rupture (Figs 9.21, 9.22)
  - In the COPLOW collection, there are 15 cases of macrophage-rich endophthalmitis in diabetic dogs with intumescent cataract and lens capsule rupture
  - Diabetic cataract often develops very rapidly in dogs, with large amounts of modified lens proteins being released into the aqueous, either passing through an intact lens capsule or after lens capsule rupture
  - The morphology of macrophage-rich endophthalmitis in diabetic dogs differs from most inflammatory diseases which occur secondary to traumatic lens capsule rupture (see Ch. 5) in that the macrophage reaction is widely distributed in the eye and not centered on the lens. There are similarities, already mentioned, to asymmetric uveitis

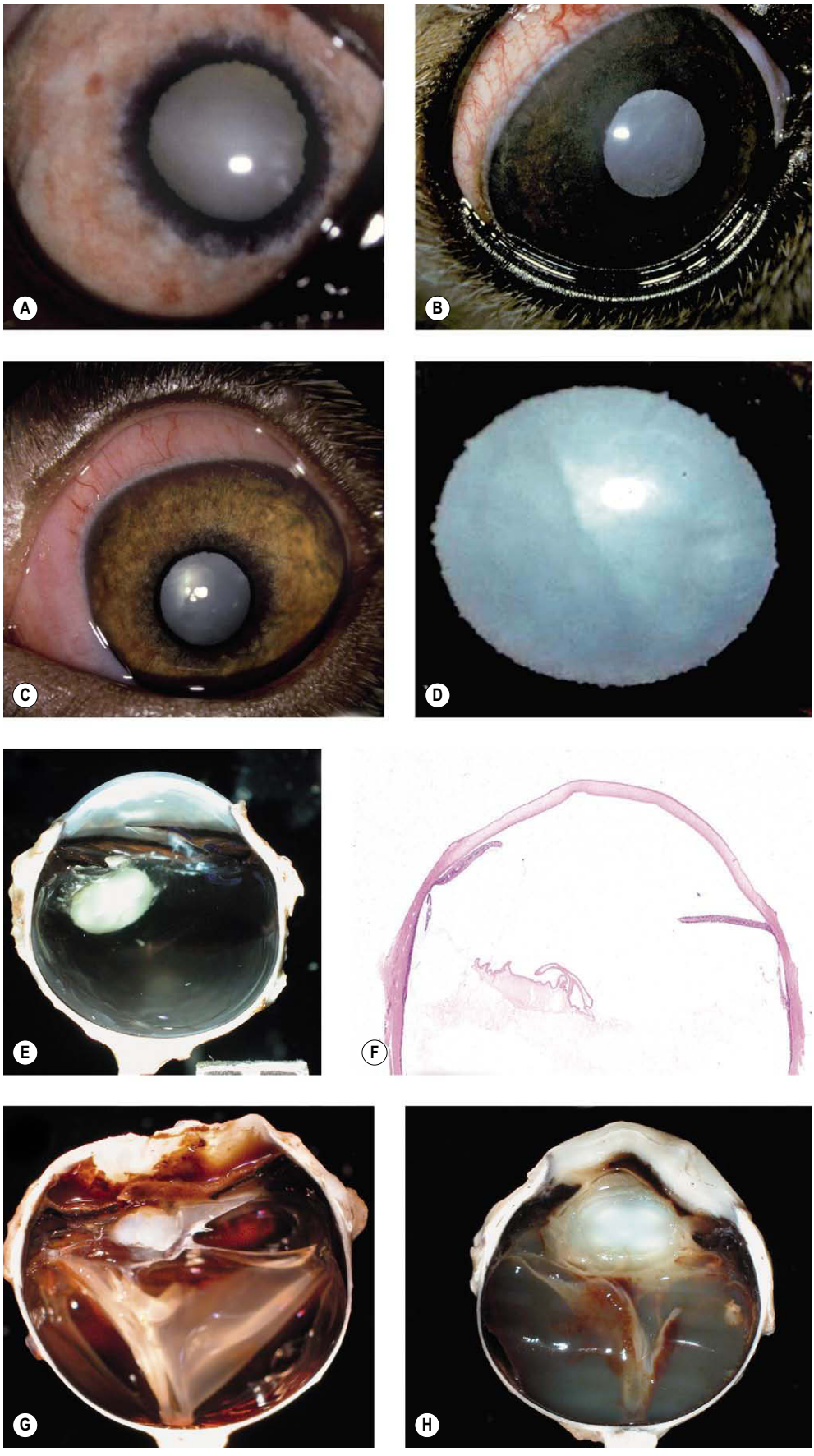


Figure 9.20 Phacolytic uveitis (lens-induced uveitis). (A) Siberian Husky, 1 year old: the iris is severely inflamed with intrastromal hemorrhage. (B) Bichon Frise, 3 years old: chronic inflammation of the iris resulted in the increased iris pigment. (C) Cocker Spaniel, 1.5 years old: the iris is swollen, and ectropion uvea is present. (D) Golden Retriever, 1 year old: the iris is heavily pigmented and ectropion uvea is present 360° at the pupil. (E) Gross photograph of a dog eye with hypermature cataract and lens-induced uveitis phacolytic uveitis). (F) Subgross photomicrograph of a dog eye with lens-induced uveitis, and the wrinkled remnants of the lens capsule in hypermature cataract. (G,H) Gross photographs of dog eyes with hypermature cataract, chronic uveitis, posterior synechia and retinal detachment with secondary glaucoma.

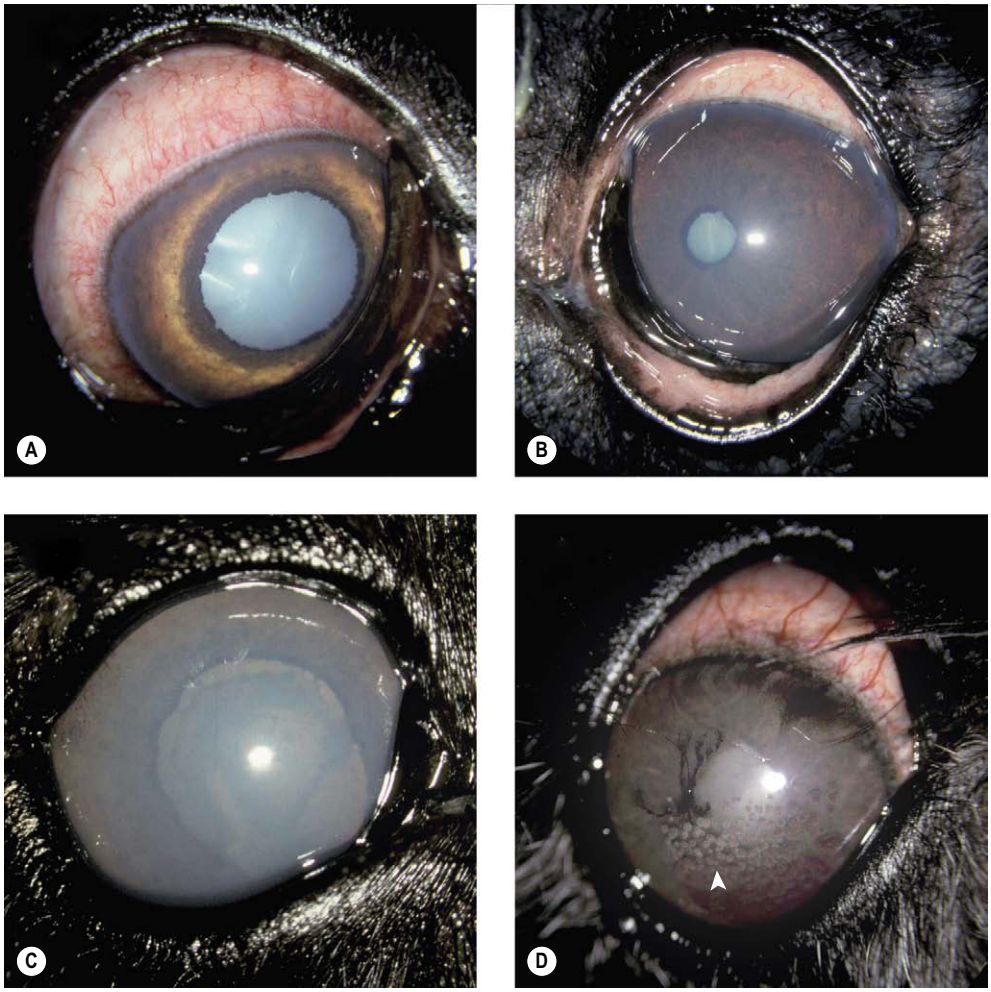


Figure 9.21 Phacolytic uveitis in diabetic cataract, clinical. (A) Black and Tan Coonhound, 9 years old: the intumescent lens can be seen. Iritis and limbal edema are also present. (B) Poodle, 10 years old: iritis with ectropion uvea is present. The pupil is severely miotic. (C) Miniature Schnauzer, 6.5 years old: severe corneal edema and lipid aqueous flare prevent visualization of the large fibrin clot in the anterior chamber and the poorly dilated pupil. (D) Miniature Schnauzer, 5 years old: the ventral endothelium has multiple keratic precipitates (arrow).

- The morphologic features of uveitis associated with diabetic cataract include:
  - Protein exudation in the anterior chamber and vitreous
  - A histiocyte-rich cellular infiltrate in the uvea
  - Histiocytic inflammatory cells on the inner retinal surface and extending into the retina.

Intraocular xanthogranuloma (Fig. 9.23)

- This rare complication of hyperlipidemia may masquerade as intraocular neoplasia
- There are five cases in the COPLOW archive, all in diabetic and hyperlipidemic Miniature Schnauzers
- All five dogs had a history, or other evidence, of chronic uveitis and secondary glaucoma
- Morphologic features of intraocular xanthogranuloma include:
  - On gross inspection, distorted, firm globes, that appear to be essentially filled with a solid, heterogeneous, light tan mass
  - The intraocular structures are effaced by a mixture of lipid-laden macrophages ('foam cells'), and Alcian blue-positive, birefringent crystals
  - Atherosclerosis of episcleral blood vessels.

Uveal involvement in systemic infections and parasitic diseases

General comments:

- Many systemic infectious diseases, including viral, protozoal, bacterial, mycotic and parasitic infections, affecting domestic species are commonly associated with ocular disease in veterinary patients
- Clinical signs referable to uveitis may be the initial reason for presentation in many of these disorders
- In addition to the systemic infectious causes of uveitis discussed in this chapter, *Bartonellosis, Brucellosis, Borreliosis, Ehrlichiosis, Leishmaniasis, Leptospirosis, Mycobacterial* infection and Rocky Mountain spotted fever, are just some of the many potential causes of infectious uveitis
- The relative importance of many systemic infectious diseases, with respect to their prevalence and clinical significance, varies widely depending on species and geographic location

We have chosen here to discuss only conditions which have been diagnosed in the COPLOW collection. We recognize that in many cases, specific infectious causes may be under-represented, because the changes seen in infectious uveitis can be non-specific making it impossible to make a specific diagnosis based on histopathological findings alone.

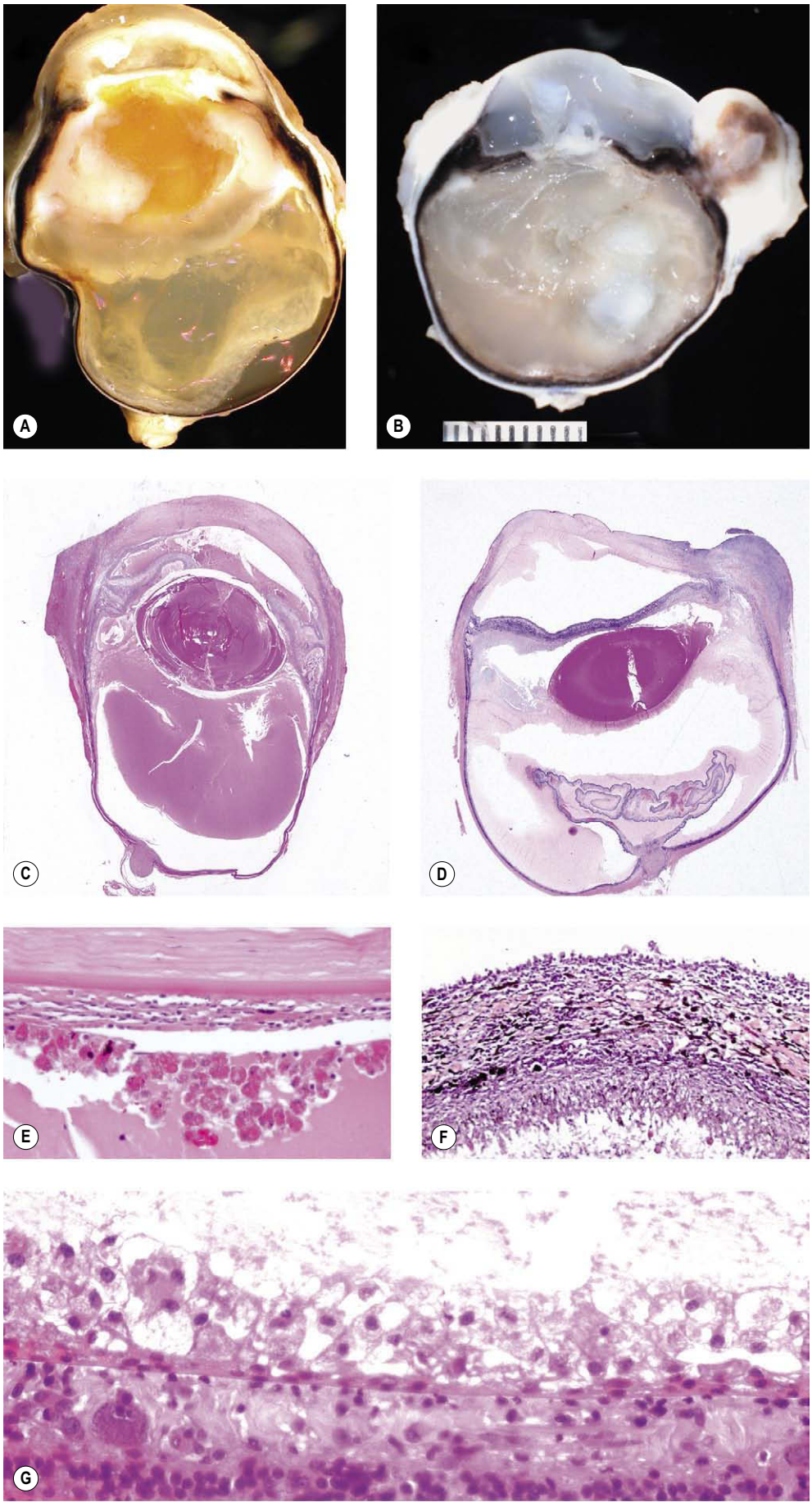


Figure 9.22 Endophthalmitis secondary to diabetic cataract, pathology. (A,B) Gross photographs of dog eyes with intense uveitis and endophthalmitis secondary to diabetic cataract. (C,D) Subgross photomicrographs of two dogs with diabetic cataract and resultant macrophage-rich uveitis. (E) Photomicrograph of an affected dog eye showing hypereosinophilic lens protein free in the anterior chamber. (F) Photomicrograph of the iris from an affected dog showing a membrane of phagocytic inflammatory cells carpeting the posterior surface of the iris, similar to that seen in asymmetric uveitis. (G) Photomicrograph of the exudates in the posterior vitreous showing many macrophage cells adjacent to and within the retina.

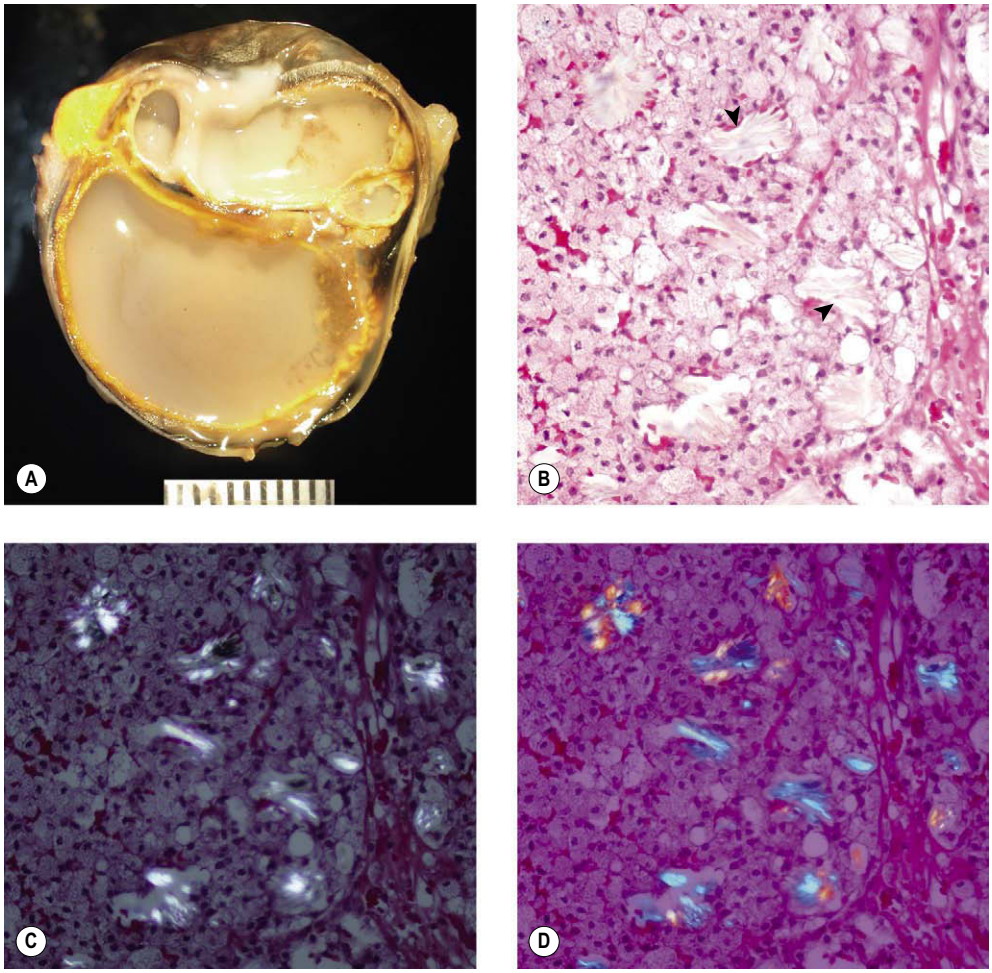


Figure 9.23 Canine intraocular solid xanthogranuloma. (A) Gross photograph of a canine globe totally effaced by a bright yellow xanthogranuloma (B) Photomicrograph of xanthogranuloma showing sheets of foamy macrophage cells and crystals (arrows) (C,D) Photomicrographs similar to (B) except using polarized light to highlight the birefringent crystals. The light in (D) is manipulated for color effect.

Feline infectious peritonitis (FIP)

There are 41 cases of FIP (Fig. 9.24) in the COPLOW collection.

- Although young cats are most commonly affected, the collection includes six cases in cats over 5 years old
- The prevalence is greatest in cats housed in multi-cat environments.

FIP is caused by a virulent biotype of feline coronavirus and is a relatively common disease that is presently incurable, and generally considered to be fatal.

Feline coronavirus infection may be limited to the gastrointestinal tract but some virulent strains acquire the ability to replicate within macrophages. In cats that do not mount an appropriate, strong, cell-mediated immune response to the virus, disseminated infection can develop, leading to FIP.

Three main variants of FIP are recognized, on the basis of their clinical and pathological presentation:

1. Effusive, 'wet' form
   - Characterized at necropsy by clear, protein rich, viscous fluid exudates in one or more body cavities and fibrinous exudates adherent to the serosal surfaces
   - Ocular involvement is less common in the purely effusive form of the disease
2. Non-effusive, 'dry' form
   - Characterized by pyogranulomatous inflammation in the parenchyma of the kidney, liver, lung or any of several other organs
   - Ocular and/or neurological involvement is often a feature of this form of the disease
3. Neuro-ocular FIP
   - This can be seen in the absence of other systemic manifestations, or in combination with the dry form of FIP, but seldom accompanies the wet form of the disease
   - Neurological involvement can occur in combination with ocular disease, or either manifestation can occur in isolation.

Morphologic features of ocular involvement with FIP:

- Although textbook descriptions suggest that histopathology is the best way to definitively diagnose this condition, as a pathologist it is always a challenge to make this diagnosis because the features of FIP are diverse and highly variable
- The COPLOW experience indicates that histopathological diagnosis of ocular FIP presents a challenge. Key to establishing a diagnosis is the recognition of the interplay of multiple different morphologic patterns, each of which adds an increment of credence to the diagnosis of ocular FIP. However, the pathologist's best effort often leads to only a tentative diagnosis of FIP.
- Gross lesions
  - One of the most important lesions indicative of FIP is the observation of highly proteinaceous, cell-poor exudates in the aqueous and vitreous body. The protein is fixed by formalin, or other fixative used, and is seen as a semisolid, translucent exudate filling the sectioned globe

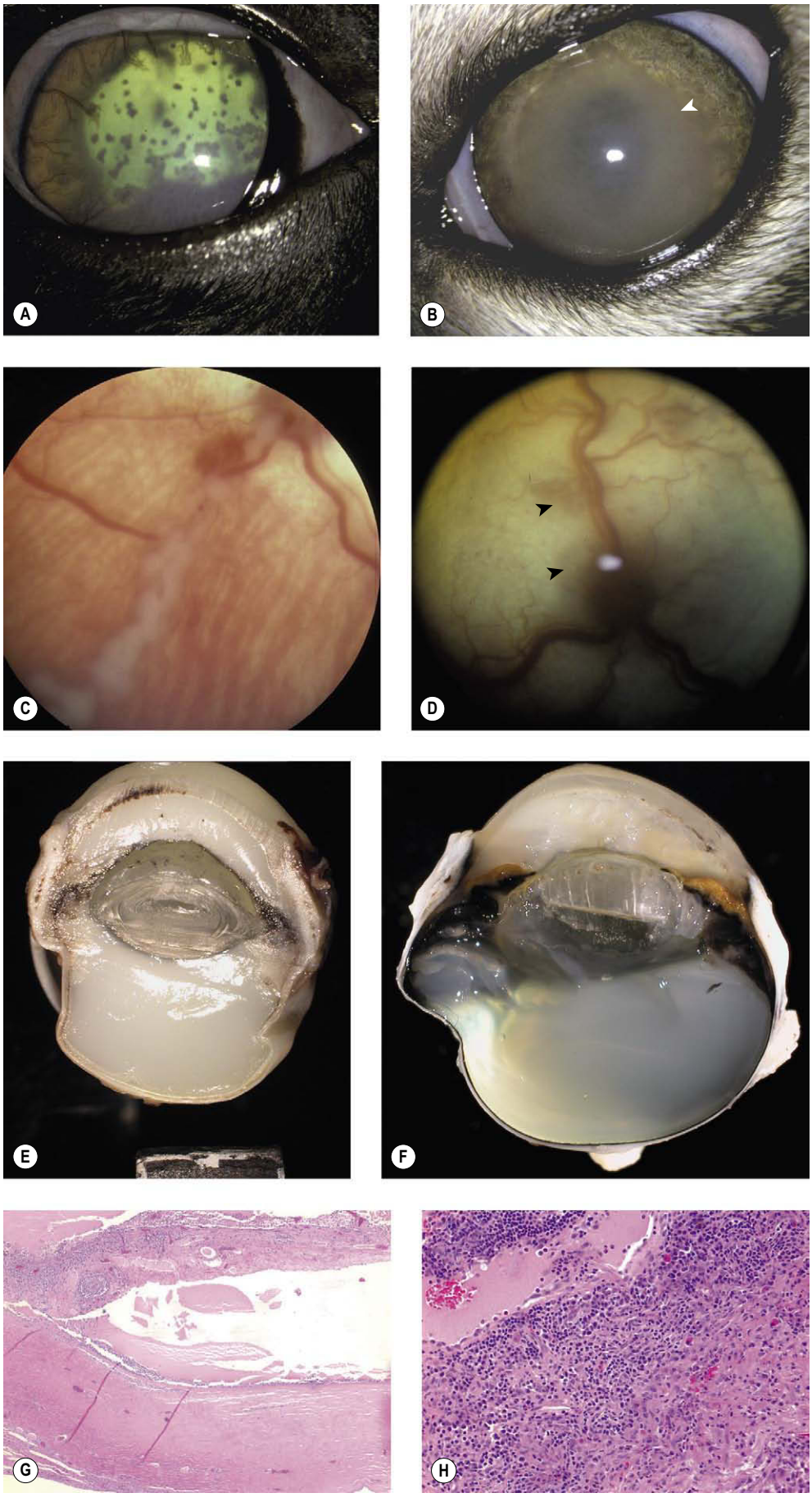


Figure 9.24 Feline infectious peritonitis (FIP). (A) DSH, 5 months old: corneal vascularization and edema are present. Multiple keratic precipitates can be seen by retroillumination. (B) DSH, 4 months old: a large fibrinous clot (arrow) fills the anterior chamber. (C) Siamese, 4 months old: the retinal vessels are dilated. Retinal hemorrhage and intraretinal white exudate are present. (D) Siamese, 5 months old: the retinal vessels are dilated, and the entire retina is edematous. Multiple areas of intraretinal exudate are present at the arrows. (E,F) Gross photographs of cat globes with feline infectious peritonitis (FIP) showing the aqueous and vitreous with a translucent and semi-solid appearance, because the high protein content of the exudates is fixed semisolid with formalin. (G,H) Photomicrographs showing the mixed nature of the cellular infiltration in FIP.

- Microscopic lesions
  - Mixed inflammatory cellular infiltrate in the uvea, retina, optic nerve and/or meninges
    - The predominant cell type is variable
    - Finding localized areas of plasma cell-rich infiltrate is helpful
    - Finding areas of suppurative inflammation is not particularly helpful in establishing a diagnosis, but relatively common in this disease
    - Finding areas of granulomatous inflammation is helpful, although not as consistent a feature as in generalized FIP in other, non-ocular sites
      - If granulomatous inflammation is found, it is helpful if macrophage cells with mildly dysplastic nuclear features are identified
      - Identifying vasculitis is an important diagnostic feature but not absolutely necessary
    - FIP is an ultimately fatal, infectious disease, so caution should be exercised in making an equivocal diagnosis without careful consideration of the clinical findings, supporting clinical pathology results and, where possible, documentation of coronavirus antigens within tissues by immunohistochemistry or PCR. However, detection of coronavirus antigens has proven to be an unreliable test in the experience of COPLOW.

Toxoplasmosis

Although toxoplasmosis is frequently cited and well documented as a cause of uveitis in cats, there are few cases of toxoplasmosis associated with uveitis in any species in the COPLOW collection.

- Most commonly reported in cats, which are the organism's host species, ocular toxoplasmosis may occur in association with other systemic signs of disease
- A number of studies also support a causal role for toxoplasmosis in some cases of uveitis in cats that show no other signs of systemic infection
  - However, the role and importance of Toxoplasma gondii infection in the pathogenesis of feline lympho-plasmacytic uveitis in otherwise healthy cats remains controversial
- Carnivorous or omnivorous species become infected by ingesting bradyzoites (tissue cysts containing hundreds of dormant organisms) in the tissues of other animals
  - Alternatively, animals may be infected by ingestion of sporozoites in foodstuffs or water contaminated by cat feces containing oocysts
  - Once ingested, these infective stages transform into tachyzoites that are disseminated in a wide range of body tissues, including the CNS, muscles, viscera, and eyes, before becoming dormant bradyzoites
- Toxoplasma gondii is reported to elicit a granulomatous and/or lympho-plasmacytic inflammatory response
- In reported cases of naturally occurring cases and in experimentally induced disease, toxoplasmosis lesions are most frequently identified in the anterior uvea, choroid and retina, and less frequently in the optic nerve.

Mycotic uveitis

- Comparative aspects:
  - Although all of these diseases occur in humans, with the exception of histoplasmosis, ocular involvement is rare
  - The 'presumed ocular histoplasmosis syndrome' in humans occurs most frequently in the Ohio River valley where histoplasmosis is common. However, the diagnosis is made based on clinical appearance, rather than by demonstrating the presence of the organism within ocular tissues
  - In humans, disseminated mycoses with ocular involvement may be encountered in immunocompromised individuals
- Blastomycosis, *Blastomyces dermatitidis* (Figs 9.25, 9.26)
  - There are 140 cases of Blastomycosis in dogs and eight cases in cats in the COPLOW collection
    - Blastomycosis is the most commonly reported disseminated mycotic infection in dogs
  - Blastomycosis is a systemic mycotic infection, most common in the Mississippi River valley. The disease is also endemic in the Ohio and Missouri River valleys and the mid-Atlantic and southern states of the United States
  - The disease occurs in very localized 'hot beds' of infection related to 'point source' exposure. Many cases live in close proximity to water courses
  - The disease is considerably more prevalent in dogs than it is in humans and more prevalent in humans than it is in cats
    - In humans, the disease seldom affects ocular structures other than the eyelid but can be associated with endophthalmitis
  - This dimorphic fungus is found in acidic soils, particularly those with decaying wood, and is infective only by inhalation of spores from infectious soil or by direct implantation into a penetrating wound. While transmission to humans from dogs is theoretically possible by this latter route, the zoonotic potential of blastomycosis is very low
  - The disease in dogs:
    - Blastomycosis is typically a disease of young adult dogs who spend a lot of time outdoors, particularly hunting or working breeds
    - The primary site of infection is the lung, which is the most commonly affected, and earliest, organ to develop lesions
    - Other organs commonly affected include the eye, skin, lymph nodes, and bone. Any other tissue may be involved occasionally
  - Morphologic features of ocular involvement in blastomycosis include:
    - Most commonly, a chorioretinitis is identified, that may be nodular or multifocal. Posterior segment involvement is most common, although the location of lesions in the globe or orbit is highly variable
    - The inflammation is pyogranulomatous in all cases, although 'classical' nodular granulomas are not typical
    - The diagnosis is dependent on finding the yeast form of the organism in histological sections or cytological preparations
    - Morphologic features of the *Blastomyces dermatitidis* organism in tissue include:
      - Exquisitely round, typically 10–15 μm diameter yeast form
      - One micron refractile cell wall
      - Broad-based, budding forms
      - Live organisms have an amphophilic central body and dead organisms have only an empty cell wall
      - Free organisms are often surrounded by Splendore–Hoeppli reaction
      - Histopathological findings in eyes with endophthalmitis related to blastomycosis do not appear to be significantly affected by anti-fungal treatment compared to untreated eyes, e.g. in their degree and type of inflammation and identification of budding yeast forms

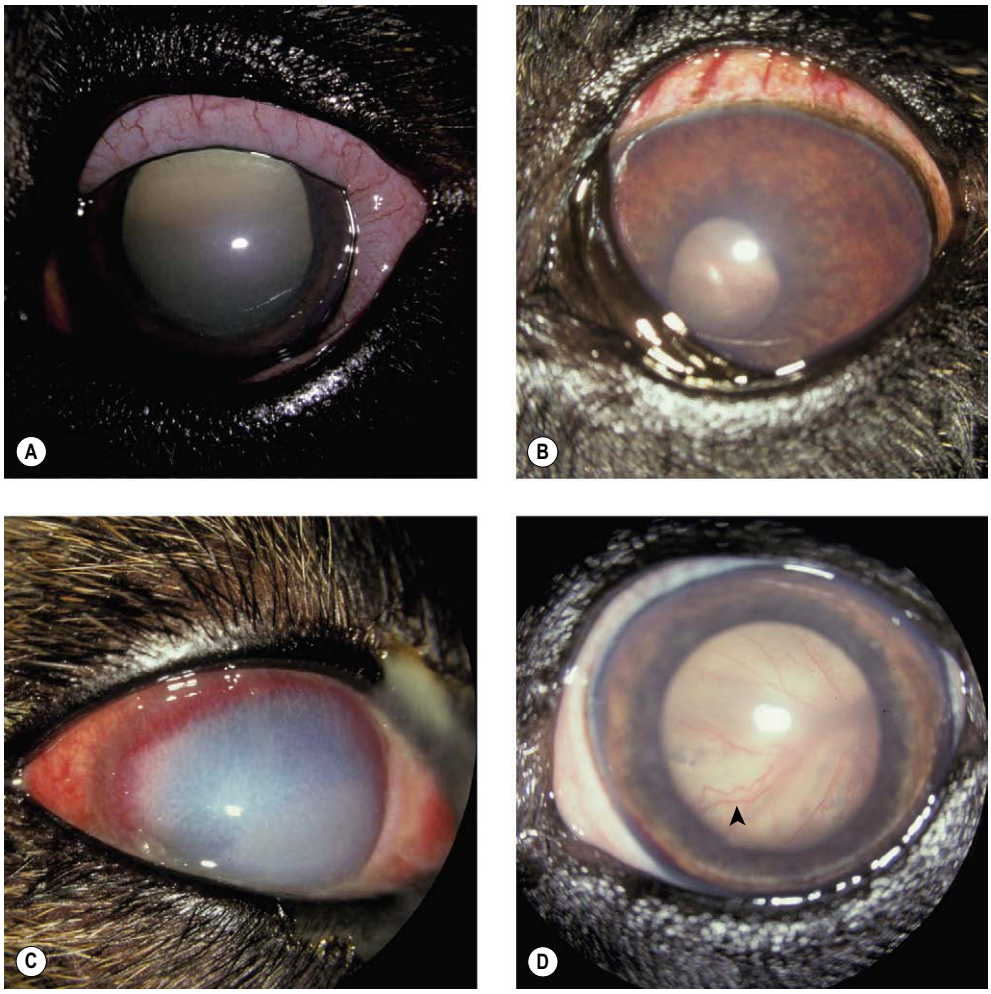


Figure 9.25 Blastomycosis, anterior segment, clinical. (A) Boxer, 3 years old: the pupil is dilated and a mild aqueous flare is present. Chemosis and a hyperemic conjunctiva are seen in this acute case. (B) Miniature Schnauzer, 5 years old: the iris is swollen and the pupil is miotic. Corneal edema and vascularization obscures the view of the leukocoria caused by the posterior segment granuloma. (C) Foxhound, 3 years old: severe corneal edema and limbal deep vessels hinder visualization of the anterior segment exudate. (D) Cocker Spaniel, 2 years old: the leukocoria is caused by the extensive subretinal exudate. Poorly-defined retinal vessels can be seen at the arrow.

- Blastomycosis in cats:
  - The disease in cats differs only minimally from that in dogs, although it is much rarer and feline blastomycosis is more likely to involve the central nervous system than canine blastomycosis

- Cryptococcosis, *Cryptococcus neoformans* (Figs 9.27, 9.28)
  - There are 12 cases in dogs and 23 cases in cats in the COPLOW collection
    - Cryptococcosis is considered to be the most common disseminated mycotic infection in cats
  - Cryptococcosis affects many species as a systemic yeast infection, but only dogs and cats with ocular involvement are represented in the COPLOW collection
  - Immunosuppression plays a role in the establishment of disseminated infection, especially in humans
  - Cats are more commonly affected than dogs but the clinical syndromes are similar in these species
  - Cryptococcosis has a worldwide distribution and is acquired by the inhalation of spores from infectious soil. The infectious stage is often a contaminant in pigeon droppings
  - The nasal cavity is the earliest and most likely site to become infected
  - The tissues of the upper respiratory tract, CNS, lymph nodes, skin, and eyes are most commonly affected by cryptococcosis
  - The definitive diagnosis of ocular cryptococcosis is dependent on identification of the organism in affected tissues or cytological preparations. Serological testing to detect cryptococcal antigen is also useful, particularly in monitoring response to therapy
  - Morphologic features of ocular cryptococcosis include:
    - Most commonly, a multifocal, granulomatous chorioretinitis, although the infection can involve any part of the eye or orbit
    - Pyogranulomatous inflammation is the most frequently observed type of inflammatory reaction. However, in some cases there is minimal cellular infiltrate
      - The degree of inflammation appears to be inversely related to the thickness of the mucoid capsule on the infecting organism
      - In cases with minimal or no inflammatory cellular component, the organisms are often found in blood vessel lumina
    - Morphologic features of the *Cryptococcus neoformans* organism in tissue include:
      - The yeast cell body ranges from 5 to 8 µm in diameter, and stains poorly with H&E, which reveals no visible internal structure
      - The central yeast is surrounded by a thick polysaccharide capsule which does not stain with H&E. The capsule is between 3 and 10 µm thick

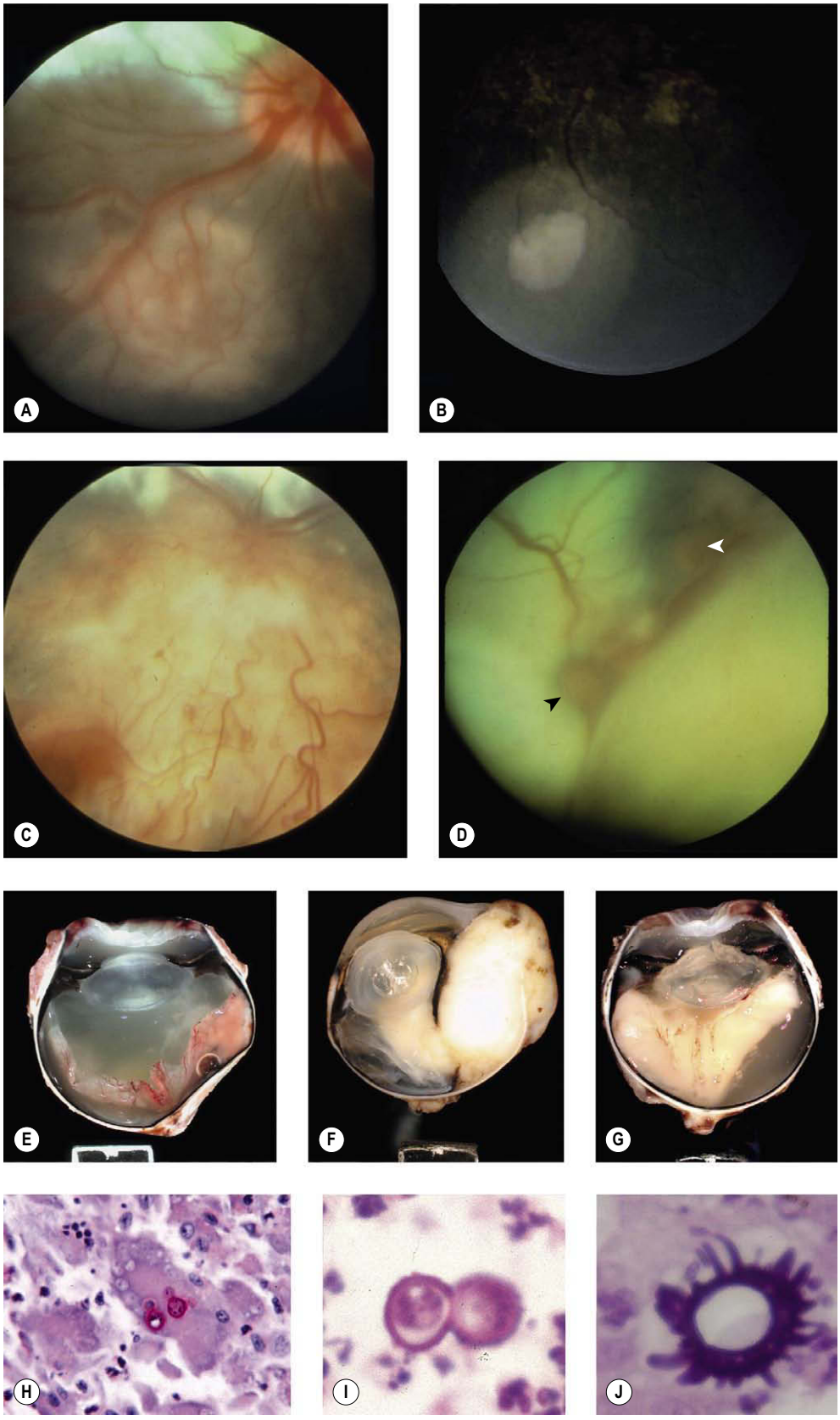


Figure 9.26 Blastomycosis, fundus and pathology. (A) Mixed Breed, 3.5 years old: the entire retina was edematous with dilated vessels. A large subretinal granuloma is present. (B) Mixed Breed, 2.5 years old: only one subretinal granuloma was found in the inferior nasal fundus. (C) DLH, 11 years old: the entire inferior retina is elevated by subretinal exudate. Retinal hemorrhage is present and all retinal vessels are tortuous and poorly defined. (D) DSH, 5 years old: the optic disc (black arrow) is poorly defined due to the total bullous detachment. Subretinal exudate is present at the white arrow. (E–G) Three gross photographs of sectioned canine globes with pyogranulomatous inflammation caused by *Blastomyces dermatiditis*. (H) Photomicrograph showing a multinucleated macrophage cell with a PAS-positive *Blastomyces* organism in the cytoplasm. (I) Photomicrograph of a *Blastomyces* organism with 'broad-based budding'. (J) Photomicrograph of *Blastomyces* yeast organism surrounded by spikes of protein, the Splendore–Hoeppli phenomenon.

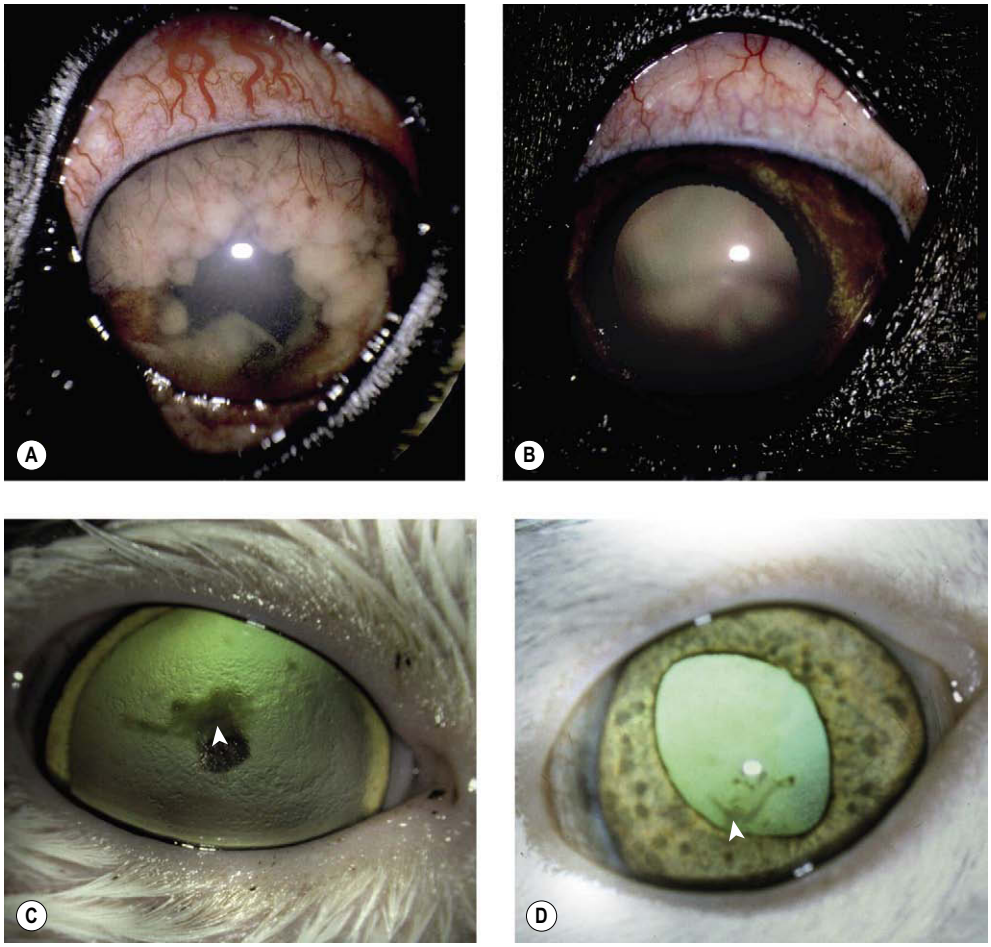


Figure 9.27 Cryptococcosis, anterior segment, clinical. (A) German Shepherd, 6 years old: white nodules of inflammatory infiltrate obscure the entire iris surface. (B) Mixed Breed, 3 years old: mild anterior uveitis with aqueous flare was present. The leukocoria is due to the totally detached retina and subretinal exudate. (C) DSH, 7 years old: aqueous flare and hyalitis were present. A white fibrinous clot adheres to the endothelium at the arrow. (D) DSH, 11 years old: the white fibrinous clot is present on the anterior lens (arrow). Many black inflammatory nodules are present in the iris.

- The central yeast organism stains magenta with PAS, and the mucoid capsule stains blue with Alcian blue, or bright red with mucicarmine stain
- In contrast to blastomycosis, budding forms will not be found in Cryptococcosis
- Very rarely, short pseudohyphae are seen.

- Histoplasmosis, *Histoplasma capsulatum* (Fig. 9.29)
  - There are two cases in dogs and 16 cases in cats in the COPLOW collection. However, the organism is often hard to find in cats, and there may be many more cases that go undiagnosed
  - Histoplasmosis is a systemic disease, occurring worldwide, that affects many species, but only dogs and cats with ocular involvement are represented in the COPLOW collection
  - The dimorphic fungus, *Histoplasma capsulatum* exists as infective hardy spores in the soil, particularly in soil rich in bird or bat droppings
  - In the USA, the disease is most common in the Mississippi and Ohio River valleys
  - The primary site of infection is in the lungs, following the inhalation of infective spores
  - Disseminated histoplasmosis commonly affects the lungs, intestine, lymph nodes, skeleton, skin and eyes, although involvement of any part of the body may be seen
  - Morphologic features of ocular histoplasmosis include:
    - Pyogranulomatous uveitis, although there is a highly variable distribution of inflammation in the globe or in orbital tissues
    - In cats there is often a thick spindle cell layer internal to the choroid as well as proliferation of the RPE. This is similar in many ways to the reaction seen in humans in the 'Presumed ocular histoplasmosis syndrome' (Fig. 9.30)
    - The diagnosis depends on demonstrating the organism within tissues, which requires PAS or a silver stain for fungus
      - The organism is always intracellular, within macrophage cells, and may be numerous or there may be only a few organisms. Furthermore there may be cases in which the organisms are too few to find, or nonexistent in the eye, as is often the case in humans
    - Morphologic features of *Histoplasma capsulatum* in tissue include:
      - The organism is small, only 3–5 µm in diameter, and is always located within macrophage cells
      - The organism has a 'target' appearance with H&E, but stains uniformly black with silver stains
      - Budding is not seen
- Coccidioidomycosis, *Coccidioides immitis* (Fig. 9.31)
  - There are 21 cases in dogs and seven cases in cats in the COPLOW collection
  - Coccidioidomycosis is a systemic disease endemic in the southwestern desert regions of the USA, as well as other low-lying deserts in Central and South America. The disease is acquired by inhalation of spores from the desert soil and animals that have prolonged outdoor exposure show enhanced risk of infection

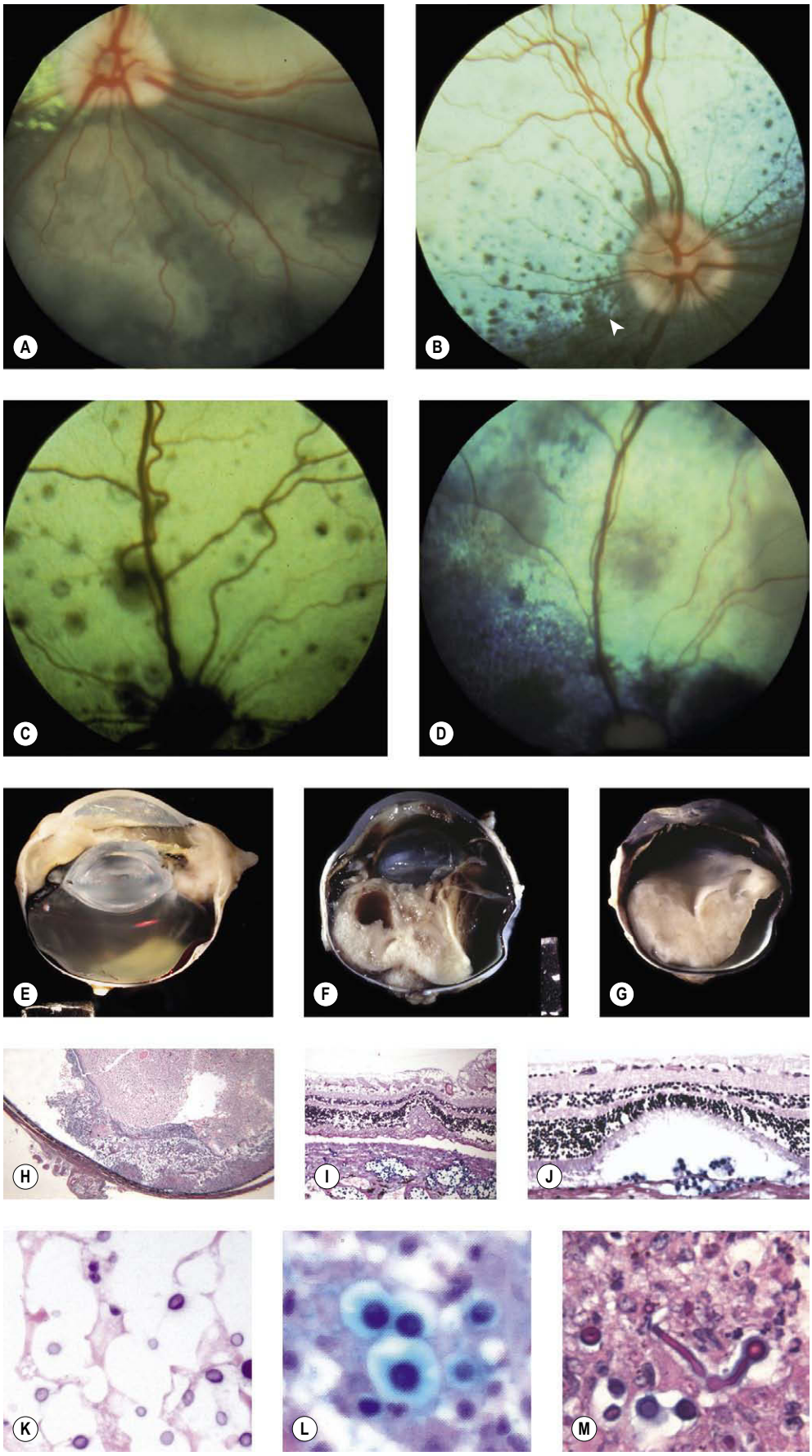


Figure 9.28 Cryptococcosis, fundus and pathology. (A) Cocker Spaniel, 6 years old: severe subretinal white exudate is present. (B) German Shepherd, 2.5 years old: the multiple dark lesions represent deep retinal exudate. Areas of peripapillary retinal edema are also present (arrow). (C) DSH, 5 years old: retinal and subretinal exudate is present as multiple foci of pigment. (D) DSH, 5 years old: multiple grey subretinal granulomas are present. (E–G) Gross photographs showing pyogranulomatous inflammatory nodules in the anterior uvea (E) and posterior segment (F,G). (H–J) Low magnification photomicrographs showing an intense chorioretinitis in cryptococcosis (H), numerous organisms in blood vessels with almost no inflammation (I), and a few organisms in the choriocapillaris (J). (K) High magnification of cryptococcal organisms showing the large non-staining mucoid capsule and the poorly stained cell walls of the organisms in the center (H&E). (L) Organisms stained with Alcian blue PAS. The mucoid capsule stains with Alcian blue and the cell walls of the organism stain with PAS. (M) PAS stain showing a pseudohyphal form of *Cryptococcus*.

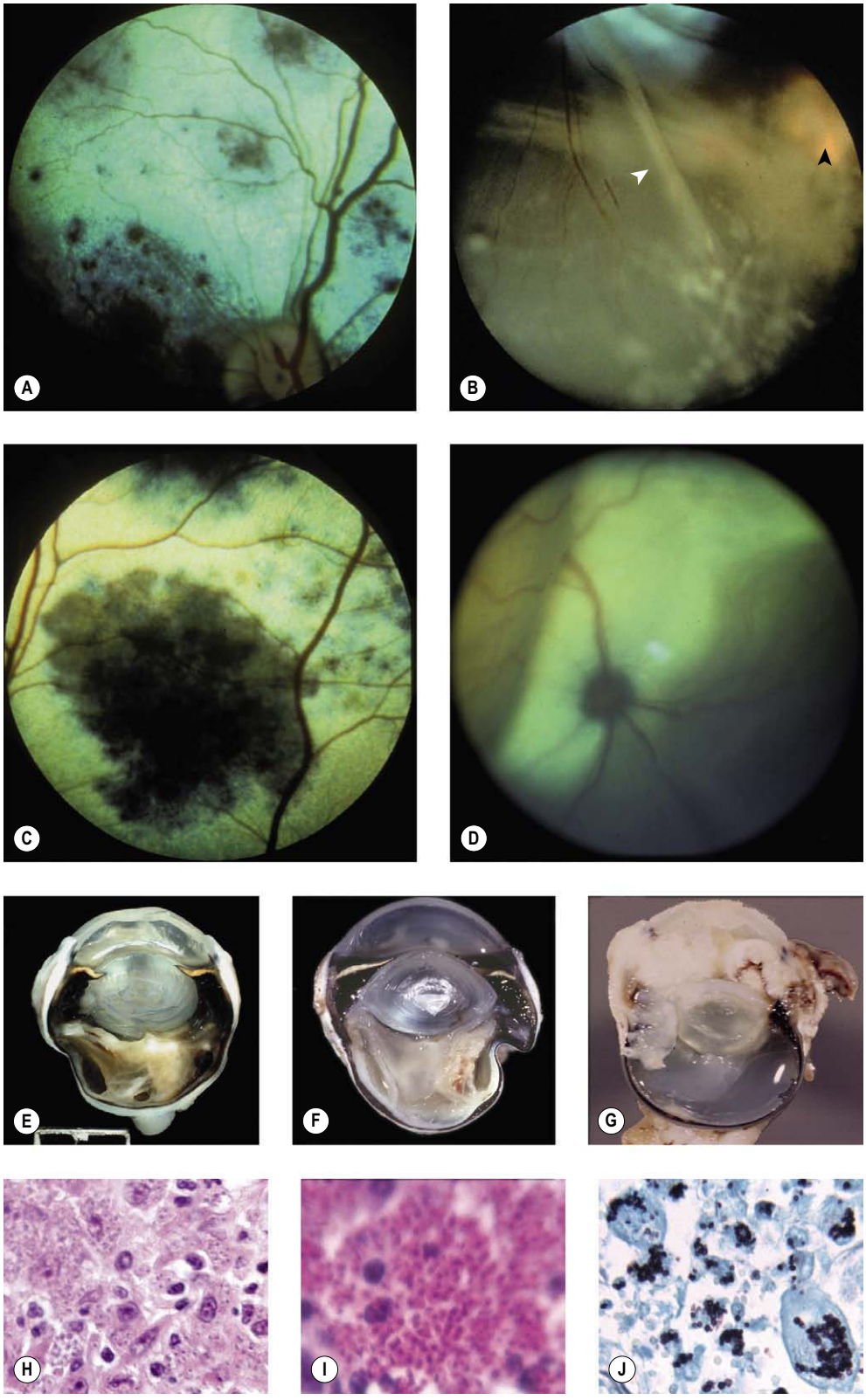


Figure 9.29 Histoplasmosis, fundus and pathology. (A) German Shepherd, 3 years old: the tapetal retina showing multiple areas of pigment proliferation surrounded by retinal edema. (B) DSH, 5 years old: The non-tapetal retina is totally detached and in folds (white arrow). In addition to the many foci of intraretinal exudate, a large subretinal granuloma is present (black arrow). (C) Persian, 6 years old: large and small areas of abnormal deep pigmentation are present. (D) DSH, 8 years old: a pink-colored subretinal exudate detached the retina superiorly and inferiorly. (E–G) Gross photographs showing pyogranulomatous chorioretinitis in cats with histoplasmosis (E,F) and anterior uveitis in an affected dog (G). (H) Photomicrograph showing numerous macrophage cells with cytoplasm rich in organisms. (I) Photomicrograph showing macrophage cells laden with PAS-positive organisms. (J) Photomicrograph showing macrophage cells containing silver-stained *Histoplasma capsulatum* organisms.

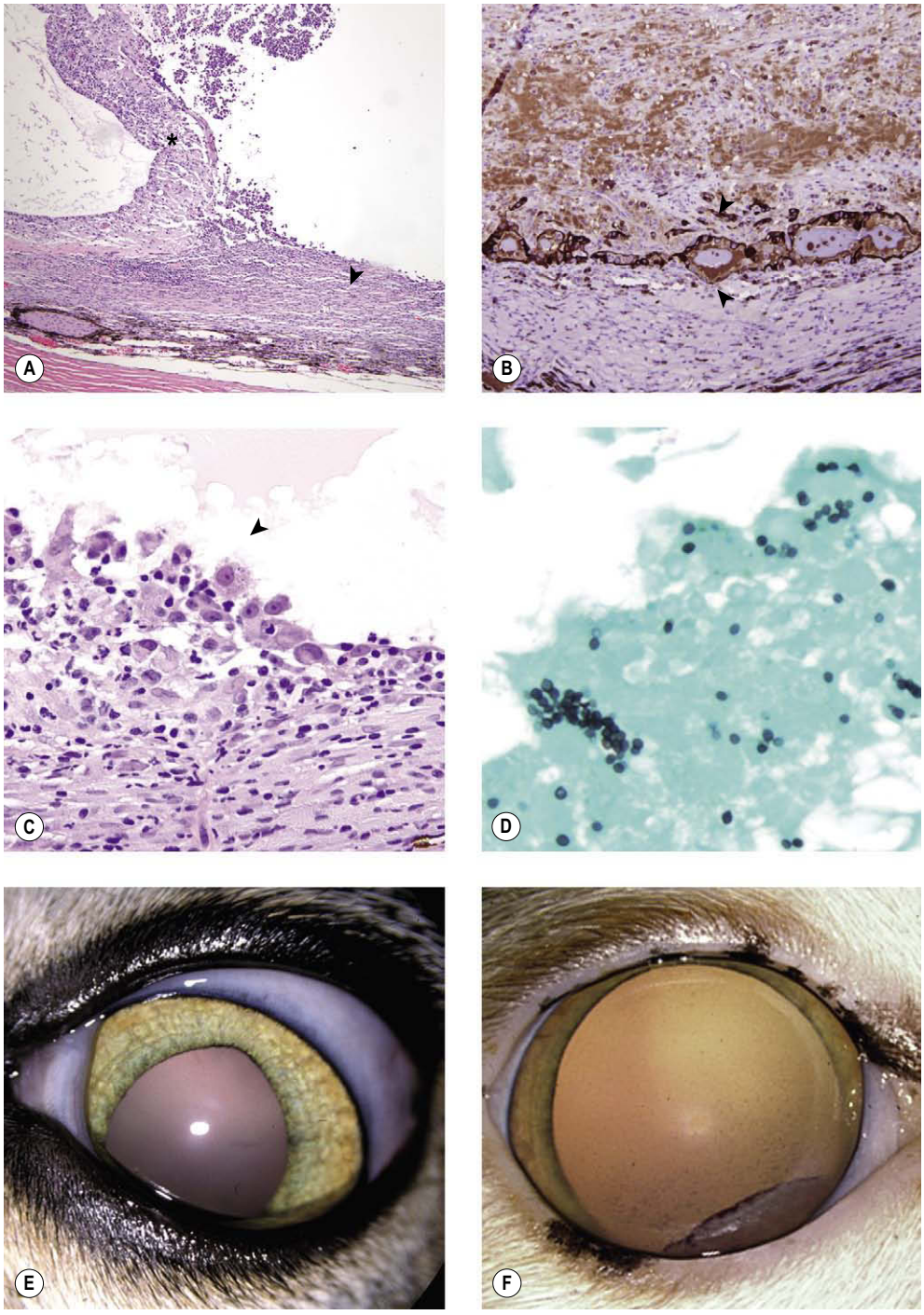


Figure 9.30 Histoplasmosis, feline, features of 'presumed histoplasmosis' (A) Photomicrograph of a feline eye with Histoplasmosis showing retinal detachment (*) and marked thickening of the inner choroid (arrow) with a combination of spindle cell proliferation and mixed inflammation. (B) Photomicrograph from the same cat as (A), showing proliferation of the RPE which is stained by immunohistochemistry for cytokeratin (arrows). (C) High magnification photomicrograph from the same cat as (A), showing macrophage cells in the inner choroid with Histoplasma organisms in the cytoplasm (arrow). (D) Histoplasmosis organisms stained with silver stain from the same field as (C). (E) Domestic shorthaired, 2 years old: leukocoria is due to total retinal detachment and subretinal granulomas. All serology and histopathology of the globes yielded no etiology. Aspirate of the submandibular lymph node identified *Histoplasma capsulatum*. (F) Domestic shorthaired, 5 years old: bilateral anterior uveitis and chorioretinitis were present. Fungal serology was negative. Histopathology identified *Histoplasma capsulatum*.

- Immunosuppressed animals are at particular risk of disseminated infection but the disease is also seen in otherwise healthy individuals
- Many species are susceptible to infection but only dogs and cats with ocular involvement are represented in the COPLOW collection
- The disease commonly affects the lungs, bones, and eyes, however any tissue may be affected
- Morphologic features of ocular involvement include:
  - Pyogranulomatous inflammation in the tissues affected. In the eye, the pattern of disease is variable, although chorioretinitis is a common feature. Ocular involvement is often unilateral
  - Coccidioidomycosis is diagnosed by demonstration of the organism in tissue sections or cytological preparations
  - The organism exists in small numbers in tissues, but it is large and easily recognized
  - The organism is more numerous, therefore more easily identified, in cat eyes than in dog eyes
  - Morphologic features of *Coccidioides immitis* in tissues include:

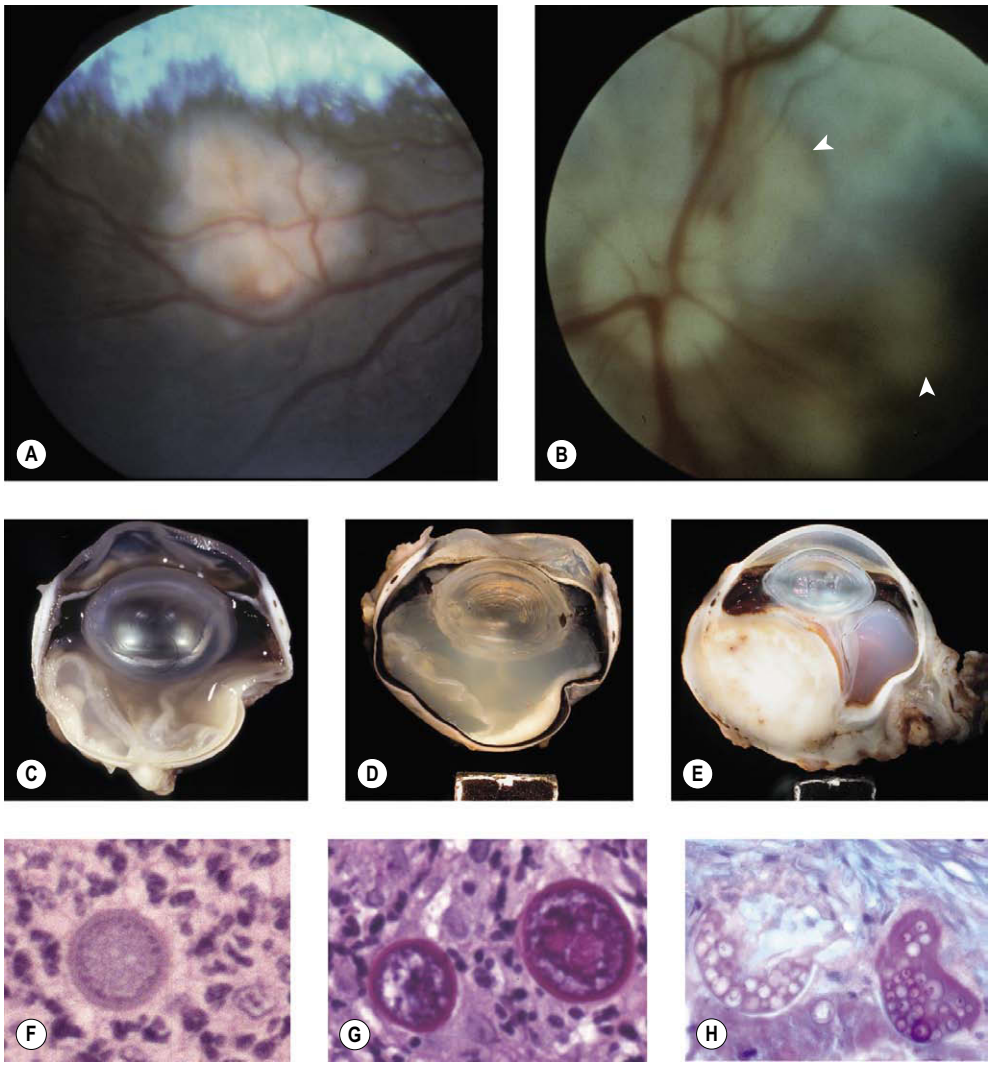


Figure 9.31 Coccidioidomycosis, fundus and pathology. (A) German Shepherd, 2 years old: a large subretinal granuloma has elevated the retina. (B) Vizsla, 3 years old: generalized chorioretinitis is present. Subretinal granulomas can be seen at the arrows. (C–E) Gross photographs of feline eyes with chorioretinitis (C,D) and a canine eye (E) with episcleral pyogranulomatous inflammation caused by *Coccidioides immitis*. The inflammatory focus in the dog eye is primarily scleral and episcleral. (F) Photomicrograph of coccidioidal endosporulating spherule (H&E). (G) Photomicrograph of spherules with developing endospores (PAS). (H) Ruptured spherule releasing endospores (Alcian blue PAS).

    - The spores from the soil, upon establishing infection in the tissues, transform into large spherules ranging from 20 to 85 µm in diameter
    - The spherules consist of a thick, refractile, outer cell wall, containing small, 2–4 µm subunits called endospores
    - Budding is not seen, but the mature spherule bursts releasing numerous endospores
- Canine systemic (disseminated) aspergillosis (Fig. 9.32)
  - In cases where the eye is submitted to COPLOW, ocular disease often precedes signs of systemic illness
  - There are 21 cases of canine systemic aspergillosis in the COPLOW collection and of these, nine are in German Shepherd dogs, a breed that appears to be predisposed to opportunistic fungal infections
  - Affected dogs have widely disseminated infection and the diagnosis carries a poor prognosis
  - Widespread vasculitis is a prominent feature of the systemic disease
  - Immune deficiency, or aberrant immune response, is thought to be important in the pathogenesis of systemic aspergillosis. The disseminated disease in humans almost exclusively affects immunocompromised individuals and patients with a history of intravenous drug abuse
  - Morphologic features of ocular disease in canine systemic aspergillosis include:
    - Panophthalmitis, often with the most severe exudate being identified, grossly and histologically in the vitreous body
    - Fungal organisms are most likely to be found in the vitreous body adjacent to the inner retina
    - Organisms are sometimes found within the lens capsule and capsular rupture may be a feature
      - The hyphae may be found directly within the lens capsule, which should therefore be carefully scrutinized, because the organisms are very apparent in this location, even with H&E stain.
    - Morphologic features of *Aspergillus* sp. in tissue include:
      - Filamentous fungi that have septate hyphae, with parallel cell walls and dichotomous branching
      - Silver stains are usually required to facilitate recognition of the hyphae
- Aspergillosis in birds
  - Although aspergillosis is a common cause of death in birds, there are only two cases of endophthalmitis and two cases of

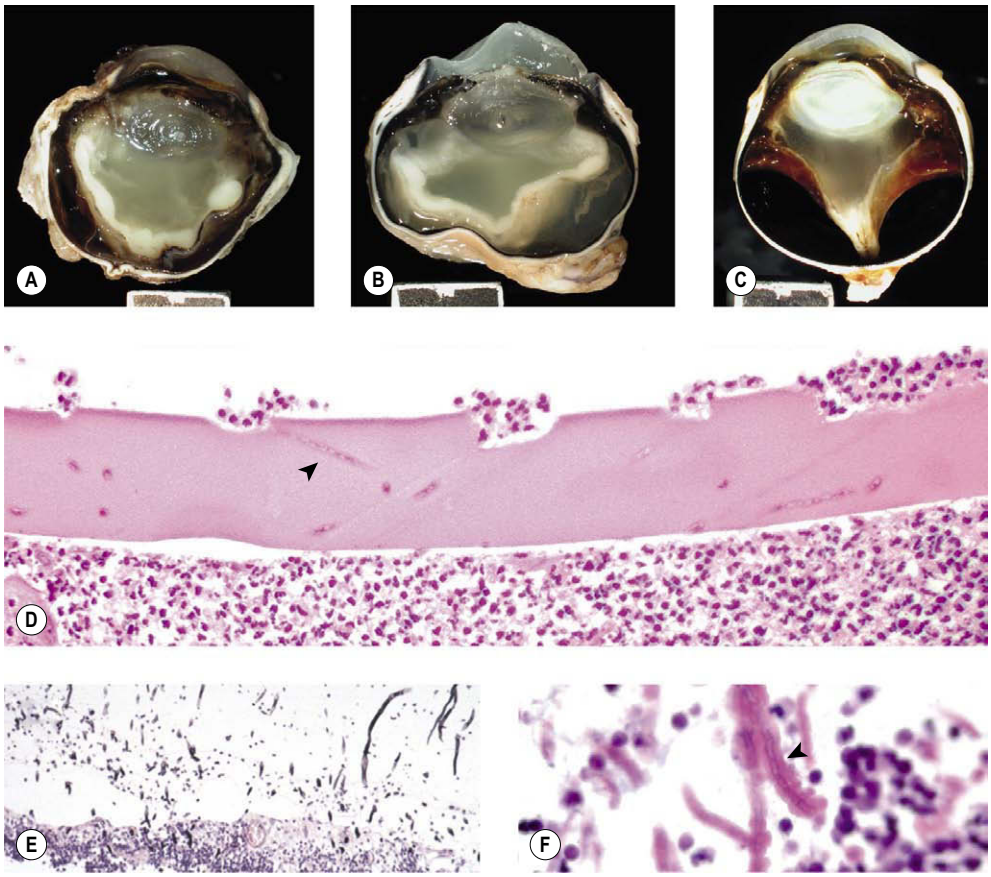


Figure 9.32 Canine systemic aspergillosis. (A–C) Gross photographs of three dog eyes showing suppurative endophthalmitis with the primary exudates in the vitreous adjacent to the retina, a feature commonly seen in systemic aspergillosis when it affects the eye. (D) Photomicrograph showing *Aspergillus* hyphae (arrow) within the lens capsule. (E) Photomicrograph showing fungal hyphae extending from the retinal inner limiting membrane into the vitreous body. (F) *Aspergillus* hyphae are surrounded by Splendore–Hoeppli (arrow) protein deposition.

keratitis associated with aspergillus infection in avian eyes in the COPLOW collection.

Canine ocular protothecosis (Prototheca zopfii *or, less often,* Prototheca wickerhamii*) (Fig. 9.33)*

There are six cases in the COPLOW collection, all in dogs.

- Disseminated protothecosis occurs in dogs and is extremely rare in other species
- The organism is classified as an saprophytic, achlorophyllous alga
- The organism is common in contaminated water but infection is rare
- Infection occurs worldwide but the South-eastern United States has a relatively high incidence
- It is postulated that systemic disease results from ingestion of the organism and invasion of the intestinal mucosa, whereas local infection occurs by contamination of skin wounds
- Clinical syndrome in dogs with systemic disease:
  - Clinical signs depend on the tissues affected, but chronic gastro-intestinal signs are often a feature
  - Ocular involvement is common in systemic disease and is usually bilateral
  - Response to treatment has been discouraging in affected dogs, and the diagnosis of disseminated protothecosis carries a poor prognosis in this species
- Morphologic features of ocular protothecosis
  - Retinal separation, often with complete, 'morning glory' retinal detachment
  - The subretinal space, vitreous, and aqueous contain a dry, granulomatous exudate but not the dense, protein-rich exudate that may be seen with many other infectious causes of endophthalmitis
  - Granulomatous inflammation carpeting the outer retina and the inner choroid
  - Large numbers of organisms are seen in macrophage cells and free within the tissue
  - Morphologic features of *Prototheca* sp. in tissues
    - One to 10 µm, round to ovoid organisms are surrounded by a thick, refractile cell wall which stains poorly or slightly amphophilic with H&E
    - A few cells undergo endosporulation and may have two or many daughter cells within the cell wall
    - The organisms stain intensely positive with PAS stain.

Canine ocular larva migrans with *Toxocara canis* (Fig. 9.34)

There are five cases of ocular larva migrans in the COPLOW collection, all in dogs.

- *Toxocara canis* was suspected to be the parasite responsible in all cases
- In most cases, larva migrans in dogs affects young, working dogs, presumably because of a large parasite burden
- Morphologic features of canine ocular larva migrans include:
  - Mild exudates in the vitreous
  - Perivascular lymphocytic inflammatory infiltrate in the retina
  - Localized granulomatous inflammation
    - It is important to search for the localized granulomas under a dissecting microscope and specifically section through the granulomatous lesions

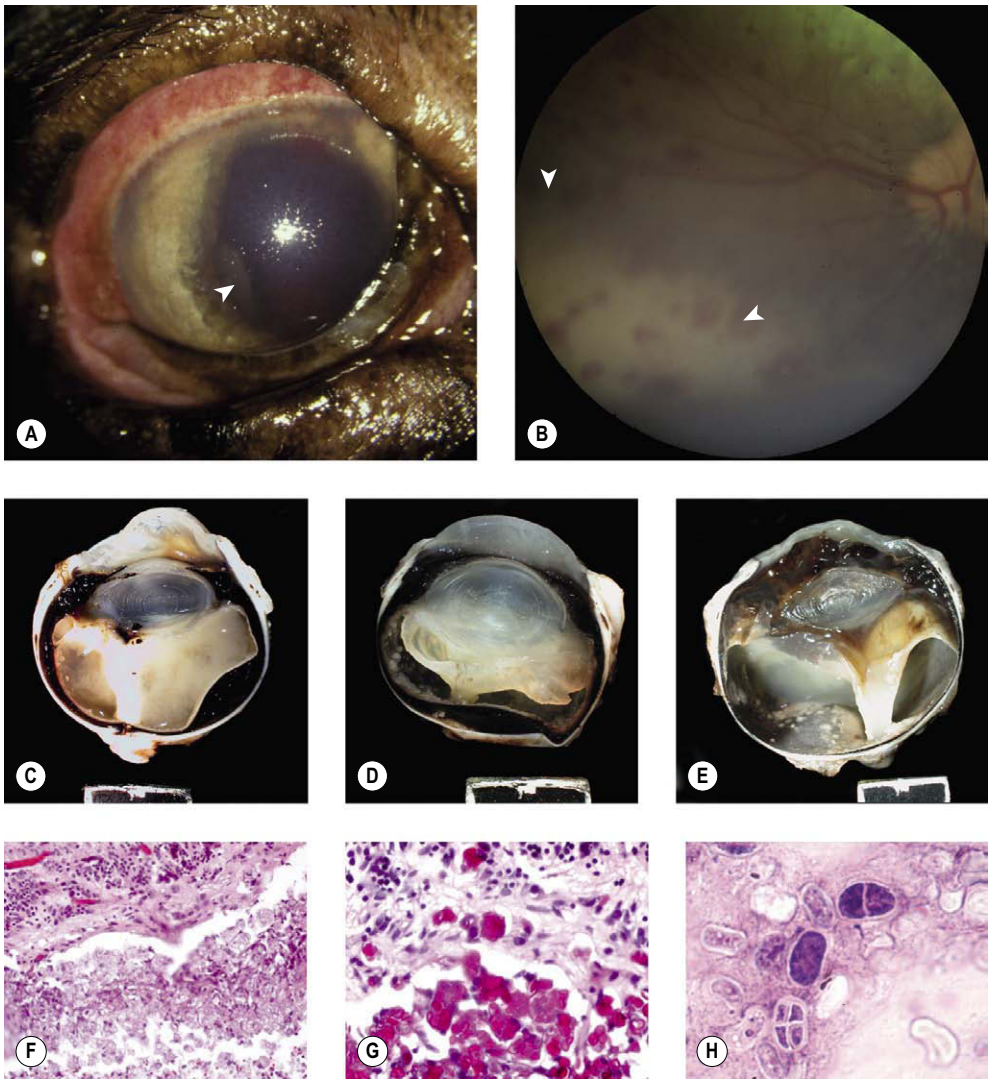


Figure 9.33 Protothecosis, clinical and pathology. (A) Labrador Retriever, 10 years old: anterior uveitis is present. The deep red tapetal reflex is due to posterior segment hemorrhage. A granuloma is seen at the arrow. (B) The left eye of the dog in (A) showing retinal edema and intraretinal hemorrhage (arrows). The large white mass represents a subretinal granuloma. (C–E) Gross photos of dog eyes affected with protothecosis. Retinal detachment and moderate exudates characterize the disease. (F) Photomicrograph showing subretinal macrophage-rich exudates. Each macrophage cell contains numerous algal organisms (H&E). (G) Photomicrograph of a subretinal exudative process showing numerous PAS+ protothecal organisms. (H) Higher magnification photograph of a touch preparation showing several organisms and the characteristic internal segmentation (Giemsa stain).

- Granulomatous lesions track in and out of the uvea, retina and vitreous
- Eosinophils are rarely seen in the cases from the COPLOW collection
- Larval parasites may or may not be found within the granulomata and they may also be found in tissues away from these lesions, particularly in the retina
- Morphologic features of *Toxocara canis* larvae in tissue include prominent lateral alae and excretory columns.

Comparative Comments

As in other species, uveitis in humans is an important and complex group of diseases. A major focus of the histopathologic study of specimens with uveitis is the determination of the cause. Uveitis may result from non-infectious stimuli, such as surgical or non-surgical trauma, and endogenous agents, including tissue necrosis and reactions to allergens. Other non-infectious causes include inflammation associated with systemic diseases and predisposing genetic factors, such as HLA antigens and allergic predispositions.

Important categories of non-infectious uveitis in humans include sarcoidosis, Behçet's disease, Vogt–Koyanagi–Harada syndrome, and phacoantigenic uveitis. A fascinating and important disease in this category that occurs only in man is sympathetic ophthalmia. This is a diffuse granulomatous inflammation of the uvea, occurring in the uninvolved eye following injury to the contralateral eye. The onset is usually a few days or weeks after a perforating injury to the exciting eye, or originally damaged eye, but there are well-documented cases of the onset being many years after the initial injury.

In infectious uveitis with a bacterial etiology, there are a number of Gram-positive organisms that have a propensity to invade the choroid from the bloodstream. Granulomatous uveitis is seen with tuberculosis, leprosy, syphilis, *Pneumocystis carinii* choroidopathy, nocardiosis, and Lyme disease. Major viral causes of uveitis in humans include herpes simplex and herpes zoster viruses, Epstein–Barr virus infection, cytomegalovirus infection, and congenital rubella syndrome. Major fungal causes of uveitis include *Candida albicans* infection, histoplasmosis and presumed ocular histoplasmosis, cryptococcal infection and *Aspergillus* infection. Causes of parasitic uveitis in humans include toxoplasmosis, toxocariasis, and onchocerciasis.

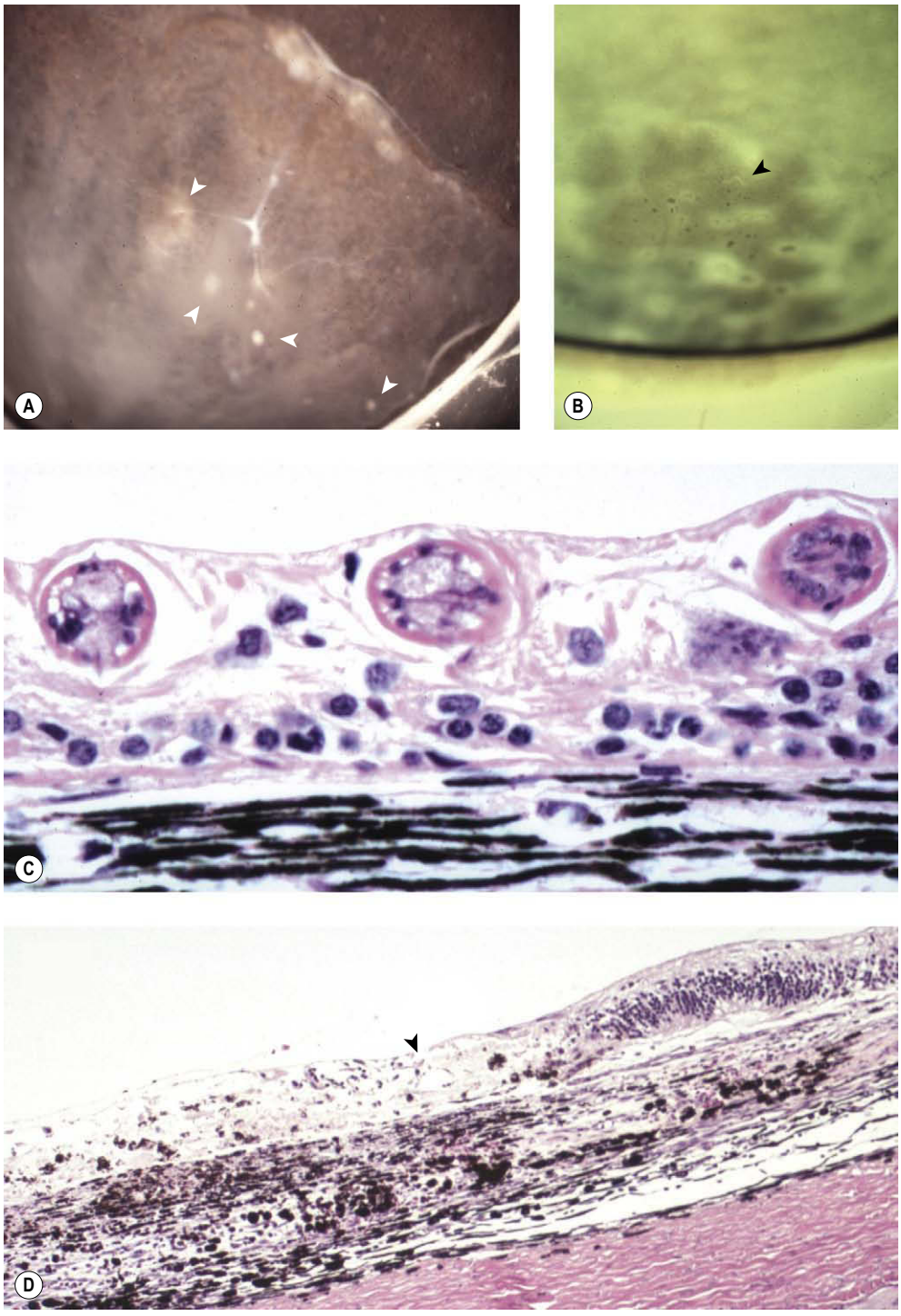


Figure 9.34 *Toxocara canis* ocular larva migrans. (A) Gross photograph of the retinal and pars plana surfaces of the eye from a young dog showing several local granuloma deposits (arrows). (B) Gross photograph of a Bouin's-fixed dog eye showing a migrating larval parasite (arrow). (C) Photomicrograph of three sections of the same larval nematode depicted in (B). (D) Lower magnification of the retina and choroid from an affected young dog showing a mixed inflammation and segmental retinal necrosis (arrow).

Canine ocular melanosis (Fig. 9.35)

There are 208 cases of ocular melanosis in dogs in the COPLOW collection:

- 50 in Cairn terriers
- 22 in Boxer dogs
- 31 in Labrador Retrievers.

Ocular melanosis in Cairn Terriers ('pigmentary glaucoma')

- The Cairn Terrier breed is prone to excessive pigmentation of the uvea, with complications which impact on ocular function
- An autosomal dominant mode of inheritance has been proposed for ocular melanosis in Cairn Terriers

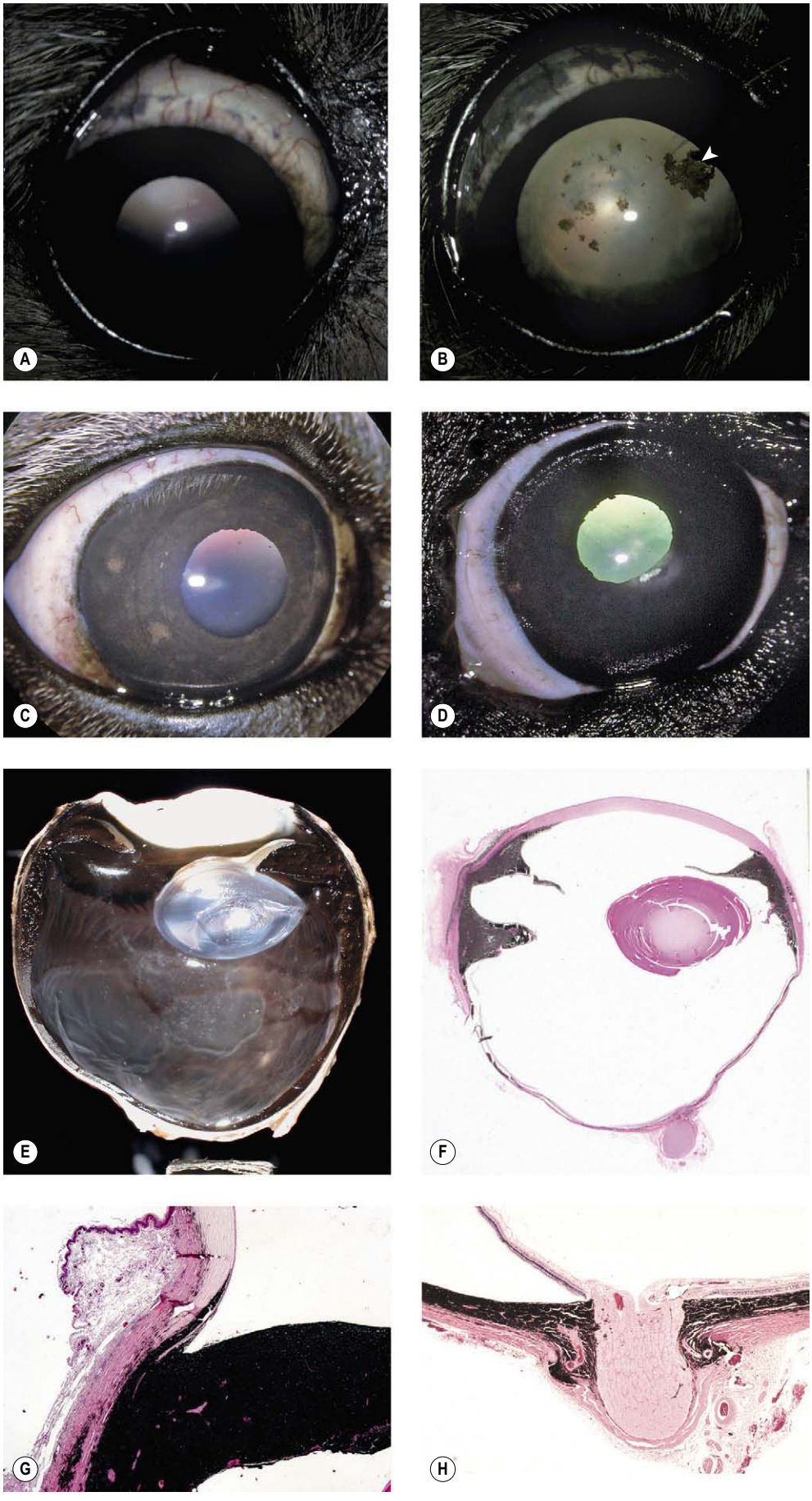


Figure 9.35 Ocular melanosis. (A) Cairn Terrier, 8 years old: the irides are extremely darkly pigmented. Focal subconjunctival pigment is present in the superior sclera. (B) Cairn Terrier, 12.5 years old: the same dog as in (A), 4.5 years later, showing increased subconjunctival pigment and pigment on the anterior lens capsule (arrow). (C) Labrador Retriever, 7 years old: iris detail was lost due to the heavy pigmentation. (D) Boxer, 12 years old: pigment infiltration totally masks iris vasculature. Increased pigment is also present at the pupil margin. (E) Gross photograph of a Cairn Terrier eye affected with ocular melanosis (pigmentary glaucoma). (F) Subgross photomicrograph of a Cairn Terrier globe with glaucoma associated with ocular melanosis. The whole uvea is hyperpigmented, but the iris base and a focus in the pars plana show dramatic nodular expansion. (G) Low magnification photomicrograph showing a heavily pigmented affected iris filled with bland round pigment-rich cells. (H) Low magnification showing a heavily pigmented choroid and optic nerve head in an affected dog.

- Age of onset and rate of progression are variable
- The disease, in Cairn Terriers is usually bilateral but often not symmetrical
- Clinical features of melanosis in Cairn Terriers include:
  - An early recognizable feature is that the iris of affected dogs is very dark brown or black and has a prominent, circumferential ridge at the iris root
  - Pigmented particles may be seen free-floating within the aqueous humor, deposited on the anterior lens capsule, or coating the endothelial surface of the cornea and opening to the drainage angle inferiorly
  - Dark pigment patches become evident in the anterior sclera and episclera
  - With progression, chronic glaucoma ensues, leading to blindness
  - In some cases, progressive pigmentation in the posterior segment may be seen, obscuring the tapetum
- Morphologic features of melanosis in Cairn Terriers
  - Diffuse over-pigmentation of the uvea
    - An increase in the size of pigmented cells and an increase in the number of pigmented cells
    - Electron microscopy and immunohistochemistry can help to distinguish if the pigmented cells are melanocytes or melanophage cells
      - Two distinct cell types can be identified within this population of large pigmented cells
      - The predominant cell type appears to be melanocytes, with different stages of melanosome development visible on electron microscopy. These cells are variably immuno-labelled using markers associated with melanocytes that include HMB45, MITF and vimentin, but not S-100 or Melan-A
      - A subpopulation of cells have the appearance of melanophages, with melanosomes contained within lysosomal membranes on electron microscopy. Some of these cells are positively immunolabelled by CD-18, indicating that they are indeed melanophages
  - Disruption of the normal uveal contour because of excessive pigmentation and excessive accumulation of pigmented cells
    - This disruption is most prominent at the iris base, anterior ciliary body and limbal sclera
  - Infiltration of pigmented cells in the limbal sclera and episclera is often quite pronounced, and contributes to a clinical impression of neoplasia
  - Acquired staphyloma is seen occasionally
  - Some affected eyes also have lympho-plasmacytic uveitis and/or PIFVM
  - Melanocytoma or malignant uveal melanoma occasionally occurs in affected eyes
  - Distinguishing melanosis from melanocytoma
    - Many pathologists consider ocular melanosis to be a diffuse variant of melanocytoma
    - At COPLOW, the distinct diagnosis of melanocytoma, rather than melanosis, is based on the finding of a regional mass, or a mass which is populated by a mixture of heavily pigmented round cells and heavily pigmented spindle cells. This combination is not seen in melanosis
- Removal of the eye is generally carried out for the management of glaucoma or to rule out neoplasia.

Canine ocular melanosis in breeds other than Cairn Terriers

- All of the clinical and morphologic features are the same as described for the Cairn Terrier, except that:
  - When ocular melanosis occurs in other breeds, it is usually unilateral
  - Based on limited electron microscopic studies, melanophages may be the predominant cell type in other breeds.

Comparative Comments

Ocular melanocytosis occurs in humans, generally as a unilateral diffuse uveal nevus, causing heterochromia of the iris and a darkened choroid, associated with gray patches on the sclera and episclera. If the eyelid and brow are involved, the condition is known as oculodermal melanocytosis. This condition carries a risk of melanoma development in Caucasians.

UVEAL NEOPLASIA

Uveal neoplasia is an important differential consideration in animals that present clinically with intraocular masses, uveitis, intraocular hemorrhage, glaucoma or retinal detachment.

Melanocytic neoplasia

- Melanocytoma in dogs (benign)
  - This is a common intraocular neoplasm in dogs.
    - There are 1090 uveal melanocytomas in the COPLOW collection
    - Of these neoplasms:
      - 94% are in the anterior uvea (Fig. 9.36)
      - 6% are in the choroid (Fig. 9.37)
  - The signalment of affected dogs may be summarized as follows:
    - The average age of affected dogs is 9.7 years
      - There is a spike in incidence in dogs under 2 years, but otherwise uveal melanocytoma is a disease of older dogs
    - Affected dogs by gender (where known)
      - Males: 169
      - Neutered males: 302
      - Females: 105
      - Spayed females: 454
    - No specific breeds are over-represented
  - Frequently, melanocytoma occurs within heavily pigmented globes or those with melanosis
  - Regardless of the extent of invasion, adequate removal by local resection, enucleation or exenteration, is generally curative
    - There are rare but notable exceptions to this generally benign biologic behavior.
      - In the COPLOW collection, there are three documented cases in which melanocytoma recurred in the orbit as malignant melanoma
    - Photocoagulation of presumed iris melanocytoma in dogs is increasingly carried out by veterinary ophthalmologists, using diode laser. Although uveal melanocytic neoplasia is generally benign in this species and this form of treatment is considered relatively non-invasive, its application in the absence of a definitive, histopathological diagnosis remains somewhat controversial. As malignant melanoma may

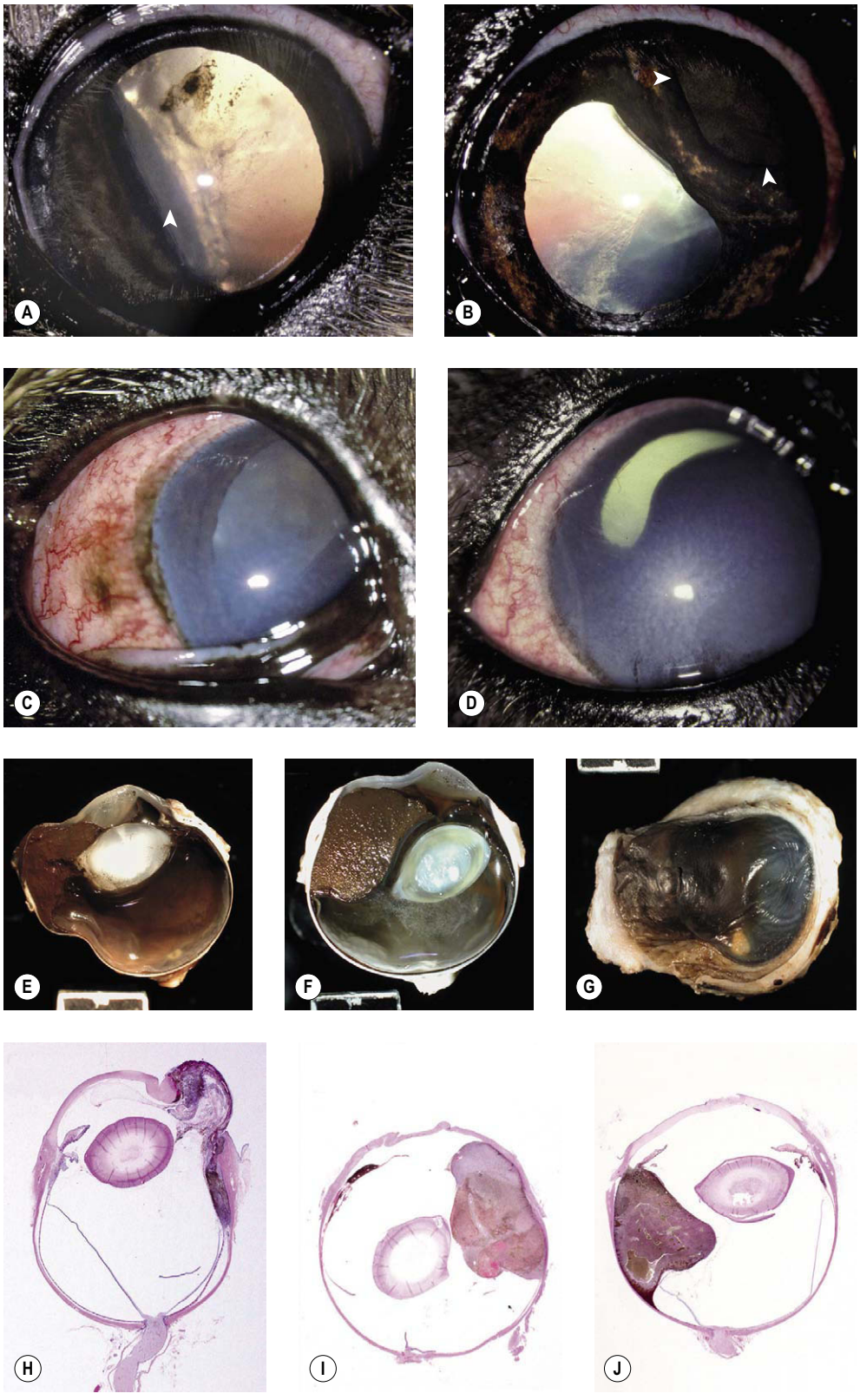


Figure 9.36 Canine anterior uveal melanocytoma. (A) Golden Retriever, 9.5 years old: the pigmented tumor appears to have originated from the ciliary body and extends anteriorly and posteriorly (arrow) to detach the retina. (B) Labrador Retriever, 10 years old: the entire iris has a blotchy pigmentation. An elevated pigmented mass (arrows) resulted in a dyscoria. (C) Mixed Breed, 9 years old: a rise in IOP and corneal edema followed the progression of this diffuse iris tumor. (D) Mixed Breed, 7 years old: this large tumor has resulted in a severe dyscoria, filled the anterior chamber inferiorly, and caused severe corneal edema. (E–G) Gross photographs of dog eyes with prominent melanocytoma within the globe and extending through the sclera at the limbus (G). (H–J) Subgross photomicrographs showing the distribution and staining pattern of anterior uveal melanocytoma. (H) Extensive tumor necrosis and a limbal scleral defect, a common feature of anterior uveal melanocytoma in dogs. These globes can perforate at the limbus, discharging semi-liquid black material.

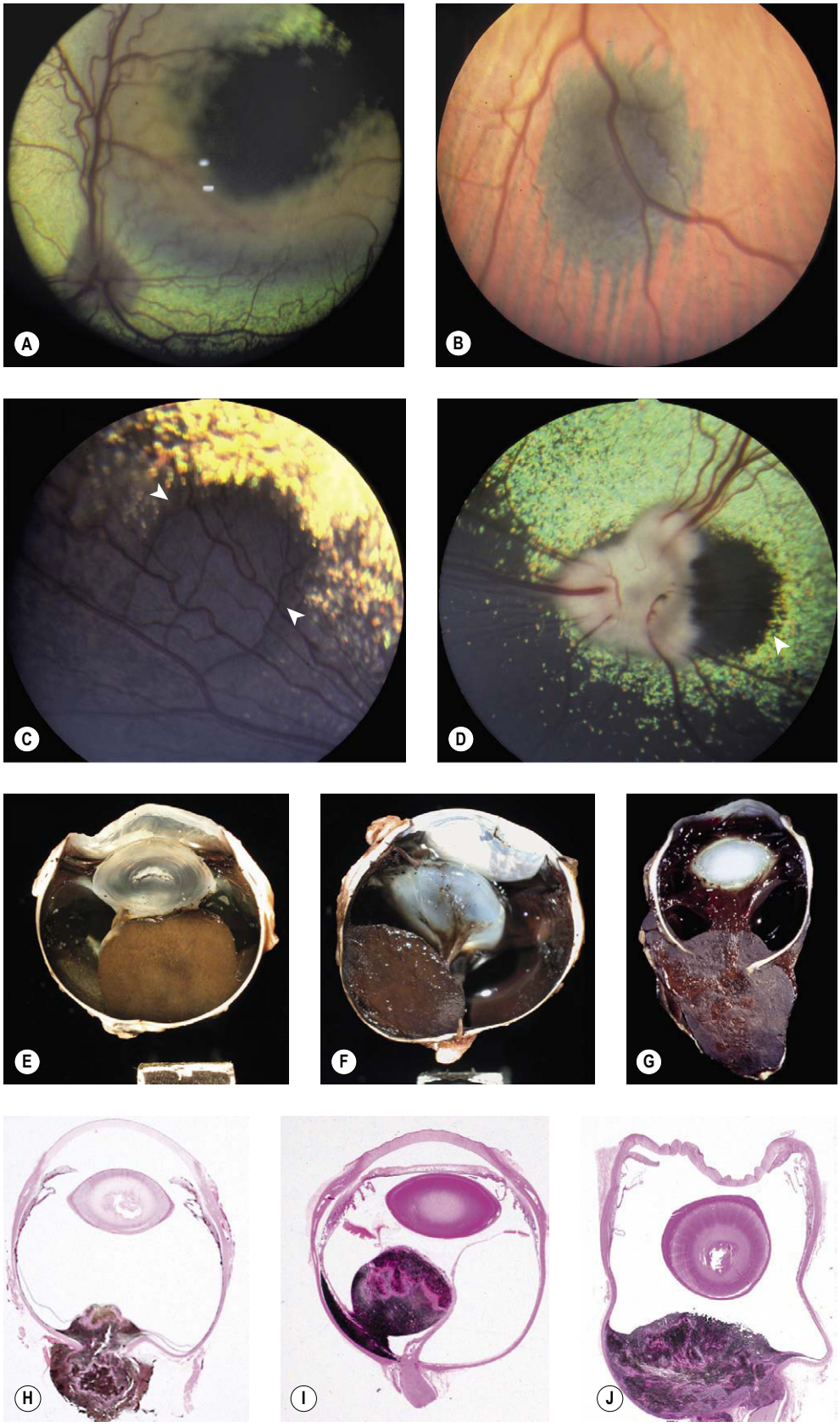


Figure 9.37 Canine choroidal melanocytoma. (A) Australian Shepherd, 7.5 years old: retinal edema and elevation surround the rapidly progressing tumor. (B) Chihuahua, 3 years old: an elevated pigmented mass is present in this albinoid fundus. (C) Shetland Sheepdog, 7 years old: the edge of the mass (arrows) is difficult to delineate from the normal choroidal pigment. (D) Golden Retriever, 8 years old: the elevated pigmented mass extends into the nerve fiber layer, represented by pigment feathering on the optic nerve and the temporal peripapillary retina (arrow). (E–G) Gross photographs showing choroidal melanocytoma with or without invasion beyond the sclera. (H–J) Subgross photomicrographs showing choroidal melanocytomas in dogs.

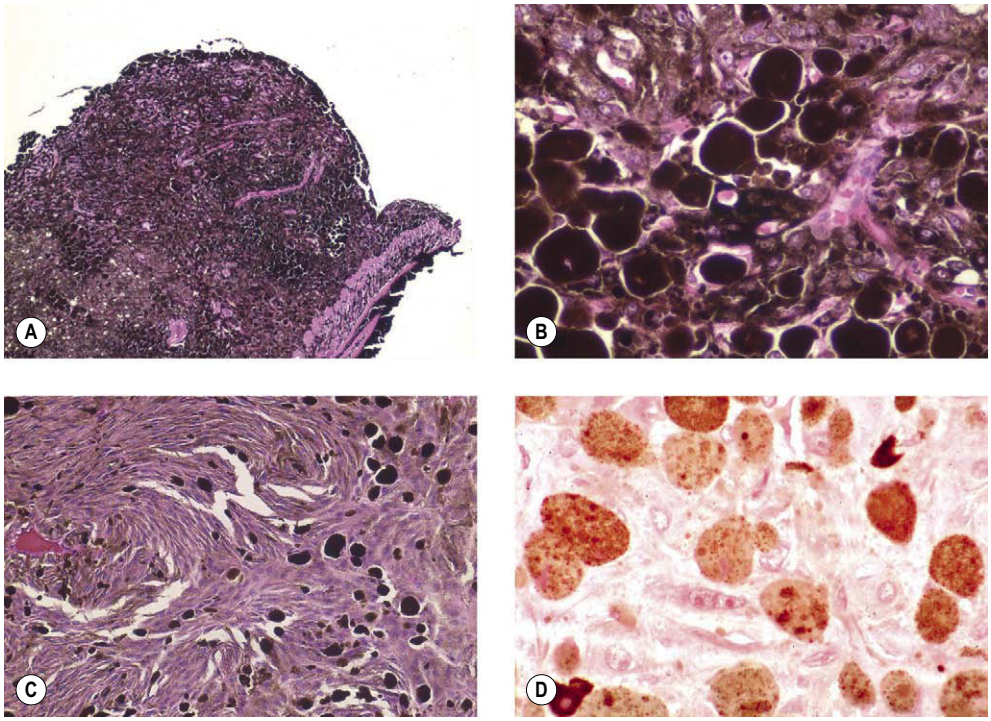


Figure 9.38 Canine uveal melanocytoma, microscopic. (A) Photomicrograph showing distortion of the papillary margin of the iris in a dog with iridal melanocytoma. (B,C) Photomicrographs showing a combination of heavily pigmented round cells and heavily pigmented spindle cells. This combination of cell types is typical of uveal melanocytoma in dogs. (D) H&E-stained 1-micron section showing the cellular features of the pigmented round cells and the pigmented spindle cells, which characterize uveal melanocytoma.

arise in eyes with melanocytoma (see below), diligent follow-up and monitoring for signs of progression is warranted following laser therapy
- Morphologic features of canine uveal melanocytoma) include (Fig. 9.38):
  - Melanocytoma is usually made up of heavily pigmented large round cells and heavily pigmented spindle cells in variable proportions
  - As the tumor takes on a more and more malignant cellular profile, more spindle-shaped, less pigmented cells begin to predominate over a smaller proportion of heavily pigmented round cells
  - The mitotic index is a valuable means of distinguishing between melanocytoma and malignant melanoma
    - More than four mitotic figures per 10 high power fields is indicative of malignant melanoma (see below) but is not necessarily predictive of malignant behavior

- Malignant ocular melanoma in dogs
  - This is less common than benign uveal melanocytoma in dogs.
    - There are 334 cases of malignant ocular melanoma in the COPLOW (Figs 9.39, 9.40)
      - 323 are in the anterior uvea
      - 11 are in the choroid
  - The signalment of affected dogs may be summarized as follows:
    - The average age of affected dogs is 10.3 years
      - In contrast to melanocytoma, there is no spike in incidence in the 0 to 2 year age group
    - Affected dogs by gender (where known)
      - Males: 37
      - Neutered males: 109
      - Females: 21
      - Spayed females: 142
  - Frequently, malignant melanoma occurs in eyes with melanocytoma
  - Even though malignant ocular melanoma is characterized by histopathological features of malignancy, few metastasize and the prognosis is therefore only slightly guarded
  - Morphologic features of malignant uveal melanoma include (Fig. 9.41):
    - Malignant melanoma is usually less pigmented than melanocytoma, or is amelanotic
    - Anaplastic nuclear features including anisokaryosis, karyomegaly, folded nuclei, and large nucleoli are characteristic
    - A mitotic index greater than four mitotic figures per 10 high power fields is indicative of malignant melanoma
- Feline diffuse iris melanoma (FDIM) (Figs 9.42, 9.43)
  - FDIM is a common clinical presentation and pathologic diagnosis in cats
    - There are 1358 cases of diffuse iris melanoma in the COPLOW collection
    - Diffuse iris melanoma accounts for 26% of total feline submissions and 50% of feline neoplasms submitted to COPLOW
  - The signalment of affected cats may be summarized as follows:
    - The average age of affected cats is 9.4 years old
    - Affected cats by gender
      - Males: 55
      - Neutered males: 643
      - Females: 65
      - Spayed females: 541
  - Clinical histories indicate that FDIM begins as focal or multifocal areas of iridal pigmentation that are gradually progressive (Fig. 9.44)
    - In the earliest stage, the pigmentation is strictly confined to the iridal surface. Lesions sampled at this stage are diagnosed as iris melanosis

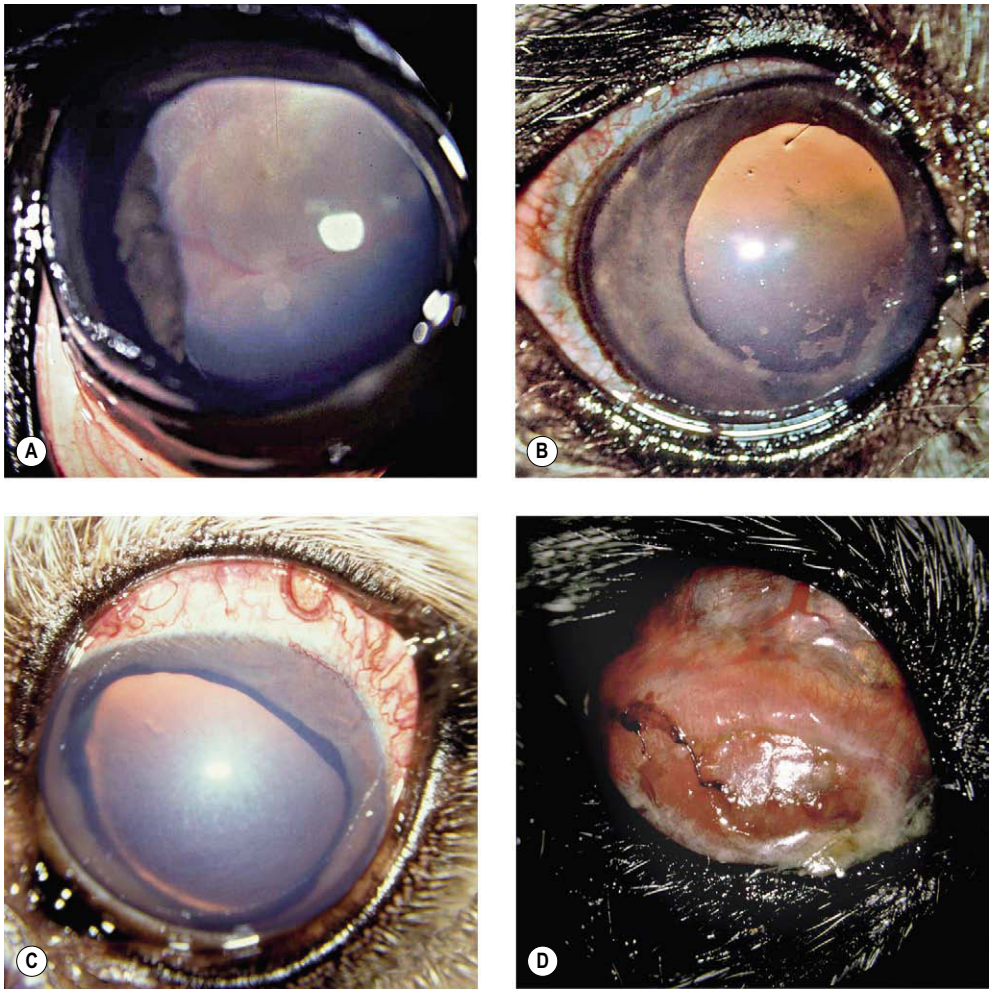


Figure 9.39 Canine uveal malignant melanoma, clinical. (A) German Shepherd Dog, 1 year old: the pigmented mass to the left progressed posteriorly to detach the retina. (B) Miniature Schnauzer, 8 years old: the entire iris was diffusely infiltrated, resulting in total loss of the fine iris detail. (C) Mixed Breed, 10 years old: diffuse iris pigmentation, especially obvious at the pupil margin, also resulted in dyscoria. (D) Mixed Breed, 11 years old: extensive intraocular involvement led to glaucoma and severe exposure keratitis of the cornea.

  - The extent of the pigmented lesions increases either by enlargement of individual spots, or by increase in the number of pigmented spots
  - The disease is designated as early FDIM when the pigment cells extend into the iridal stroma but the extent of involvement is still entirely within the iris
- The progression of disease is highly variable
  - Cases have been documented where the disease has slowly progressed over a 10-year period with little or no apparent effect on the health of the eye, or where FDIM has gradually led to glaucoma
  - Other cases progress rapidly, developing glaucoma and metastases over a short timescale (Fig. 9.45)
  - At this time, there is no good way to predict the likely progression of disease in individual cats
- This unpredictable progression makes it hard to offer advice on when to enucleate:
  - Some clinicians will remove a globe when they document any evidence of continued growth and progression of pigmented lesions, while others will wait until glaucoma develops
  - Cats with early FDIM at the time of enucleation, that generally have not yet developed glaucoma, survive at the same rate as unaffected cats
  - It is very difficult to accurately estimate the rate of metastatic disease in affected cats. Obtaining documented evidence of metastatic disease may be confounded by long periods of latency in many cases
    - Most cats with documented metastatic disease had advanced disease, i.e., Extension of the neoplasm beyond the iris and/or neoplastic cells within the scleral venous plexus, at the time of enucleation
  - Metastasis occurs more often to the abdominal cavity/abdominal organs than to the lungs
  - Recurrence in the orbit may also occur
- FDIM demonstrates a tremendous degree of variation in cellular morphology. Within this spectrum of disease, a number of histopathological variants are recognized (Fig. 9.46):
  - Round cell or polygonal cell
    - Most common
  - Spindle cell
  - Balloon cell
    - Large melanocytes with vacuolated cytoplasm and round, central nuclei
  - Anaplastic variants
  - Giant cells

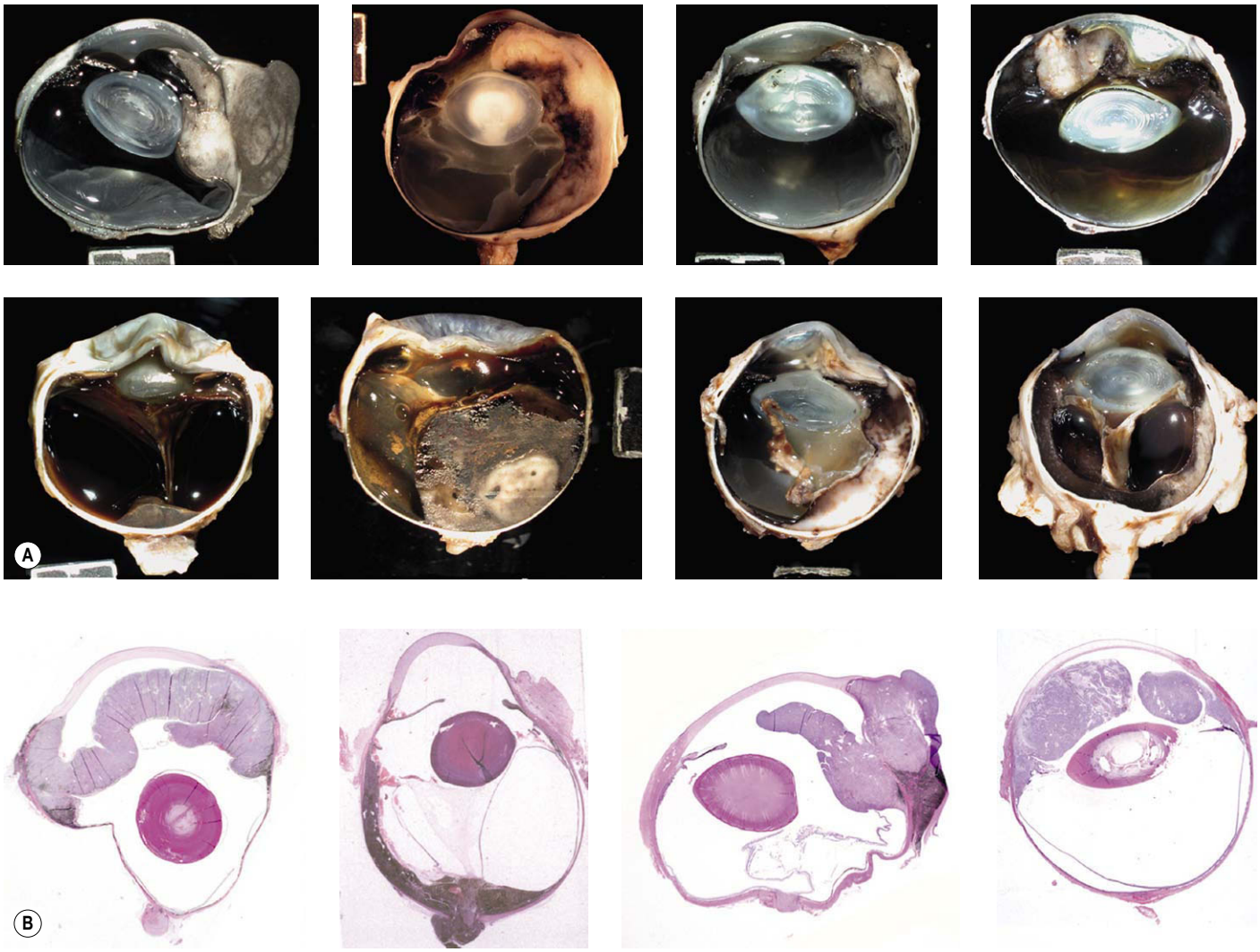


Figure 9.40 Canine uveal malignant melanoma, pathology. (A) A montage of eight gross photographs of canine globes that contain uveal malignant melanoma. Note the variation in the extent of pigment in the tumors. (B) A montage of four subgross photomicrographs showing canine globes with anterior or posterior uveal malignant melanomas.

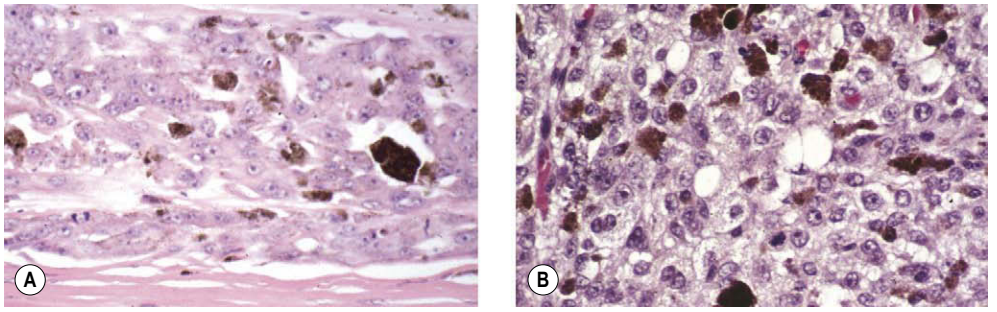


Figure 9.41 Canine uveal malignant melanoma, microscopic. (A,B) Photomicrographs of sections from two dogs with uveal malignant melanoma showing characteristic features of malignancy, including mitotic figures and atypical chromatin distribution.

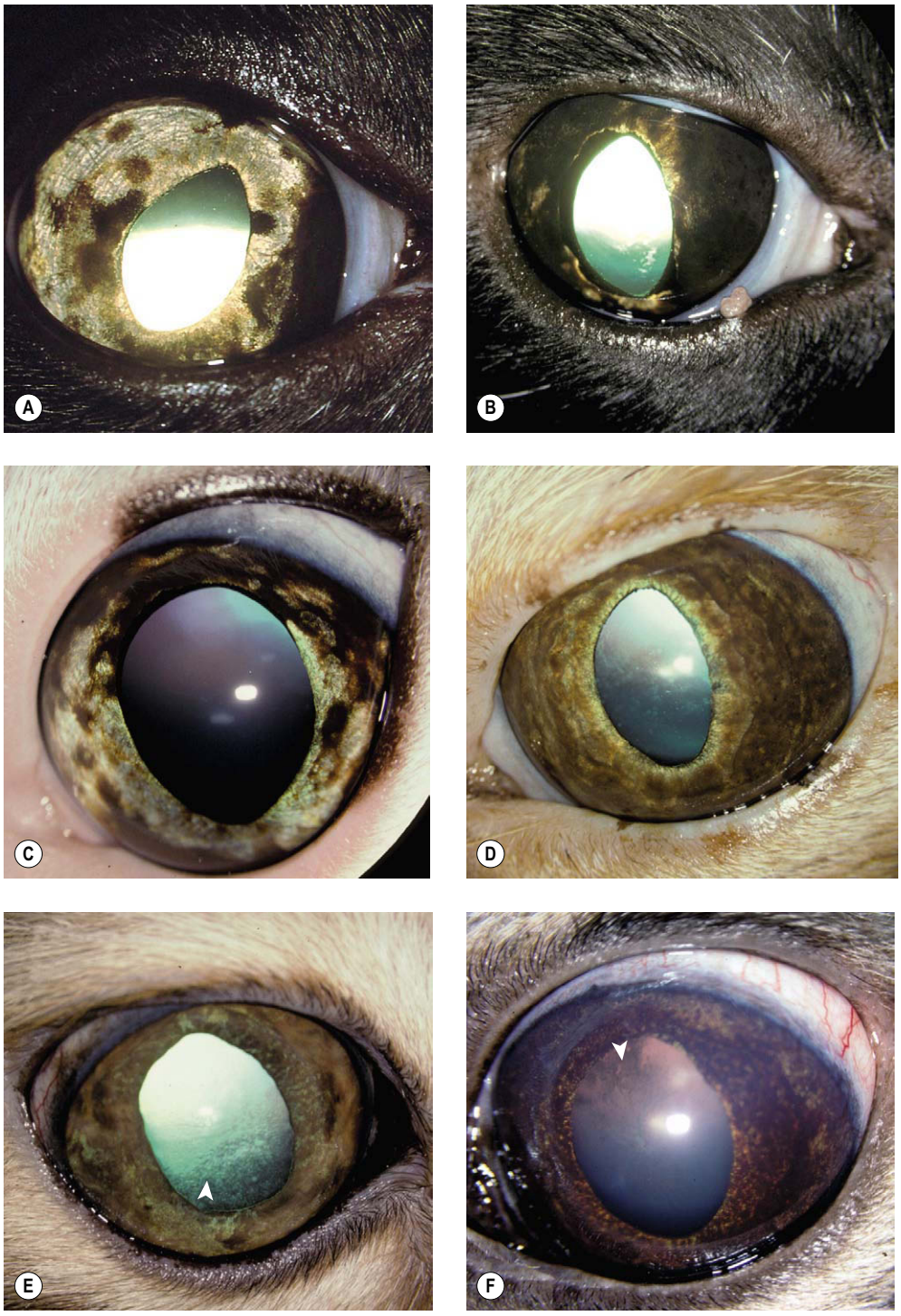


Figure 9.42 Feline diffuse iris melanoma (FDIM), clinical. (A) DSH, 9 years old: multiple foci of abnormal pigment are present. Mild elevation of the iris was noted nasally. (B) DSH, 12.5 years old: this is the same cat as in (A), 3.5 years later. Increased pigment plus elevation of the iris due to the infiltration are present. (C) DSH, 12 years old: diffuse pigmentation is present throughout the iris. (D) DSH, 15 years old: this iris is diffusely heavily pigmented. (E) Maine Coon Cat, 13 years old: the iris is diffusely pigmented with focal areas of increased pigment. Dyscoria is present and the mottled tapetal reflex represents pigment (arrow) on the anterior surface of the lens. (F) DSH, 16 years old: the heavily pigmented and infiltrated iris has resulted in a secondary glaucoma. Pigment is present on the anterior lens surface (arrow).

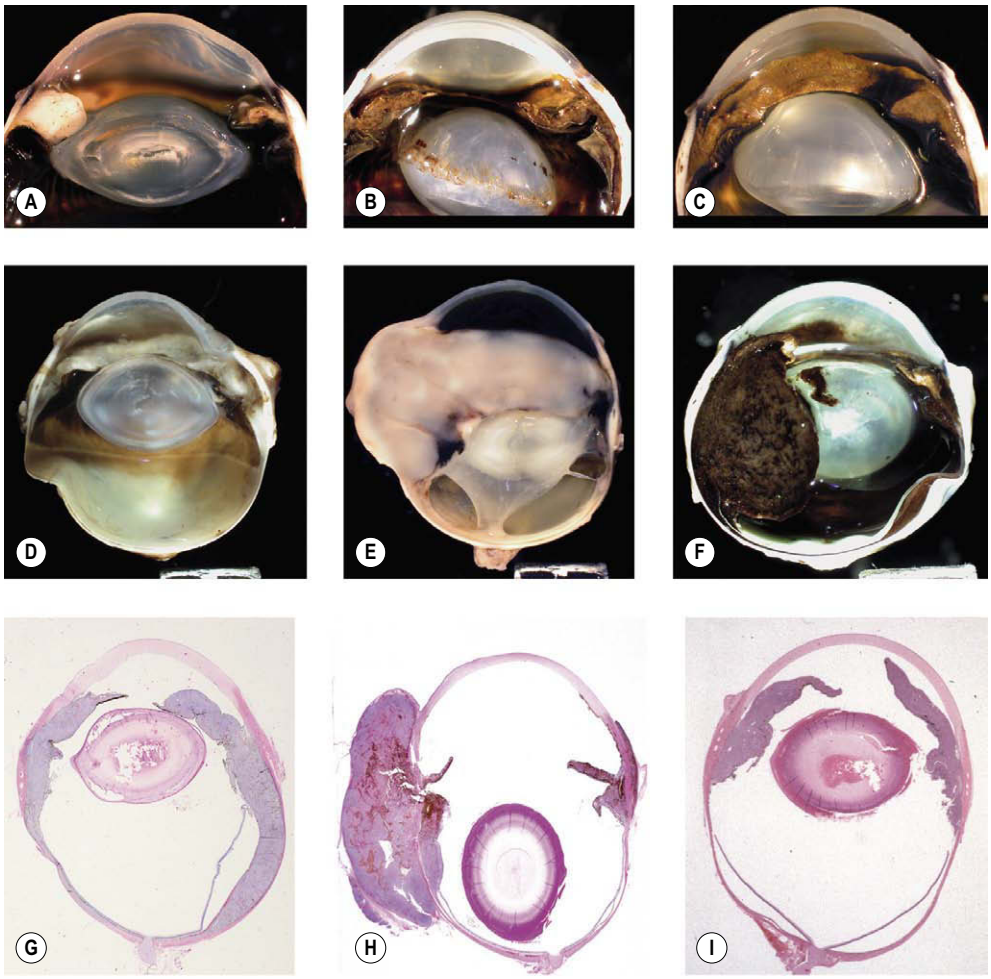


Figure 9.43 Feline diffuse iris melanoma (FDIM), pathology. (A–F) Gross photographs of feline globes with variable degrees of involvement with feline diffuse iris melanoma (FDIM). Greater involvement increases the risk of metastatic disease. (E) The globe from a blue-eyed Siamese cat with an amelanotic tumor, which would be expected. (F) A globe with an atypical distribution. (G–I) Subgross photomicrographs showing FDIM to variable degrees. The globe in (H) has atypical distribution, because the tumor is not diffuse.

  - Amelanotic variants are often clinically mistaken for inflammatory disease
  - Not all cases are strictly diffuse in the iris. Variations in tumor distribution occur where the neoplasm exists as solid localized masses or other cases which are primarily in the ciliary body or even the choroid
  - Although uveal melanomas have been experimentally induced in cats by feline sarcoma virus infection, there is no compelling evidence to support an important role for retrovirus infection in the spontaneous development of feline anterior uveal melanoma
- Feline atypical melanoma (Fig. 9.47)
  - This is an uncommon variant of uveal melanoma in cats:
    - There are only 23 cases in the COPLOW collection, representing only 1% of feline neoplasms in the collection
  - These are multifocal masses composed entirely of very heavily pigmented round cells, with bland small round nuclei only visible on bleached sections
    - The tumors are distributed throughout the uvea and may involve the iris but, in contrast to FDIM, they are not centered on the iris
    - A characteristic feature, seen in most cases, is the appearance of aggregates of tumor cells on the retinal pigment epithelium, filling the sub-retinal space and extending into the retina
  - Despite the bland cellular features, several of these neoplasms have metastasized
- Equine anterior uveal melanocytic neoplasms
  - There are 17 cases of equine intraocular melanocytic neoplasia in the COPLOW collection
  - Although dermal melanocytic neoplasia is common in horses, equine ocular melanocytic neoplasms are rare, with few reports in the veterinary literature
  - Reported cases have generally shown benign histological characteristics.

Comparative Comments

Uveal malignant melanoma is the most common primary intraocular tumor in adult humans, with an incidence in the United States of approximately six cases per million. These occur predominantly in the choroid (85%) with about 10% in the ciliary body and 5% in the iris.

Except in the iris, uveal malignant melanoma is a highly aggressive tumor, and about half of patients with this type die with metastatic disease within 10–15 years of diagnosis.

In 1931, Colonel George R. Callender at the Armed Forces Institute of Pathology classified these tumors into six types, based on the morphology of the tumor cells. A modified Callender classification continues to be used for the cytologic classification of these tumors.

- The major categories are spindle cell nevus; spindle cell melanoma; epithelioid melanoma; and mixed-cell type (mixture of spindle and epithelioid cells). This classification has proved less useful in tumors in other species.

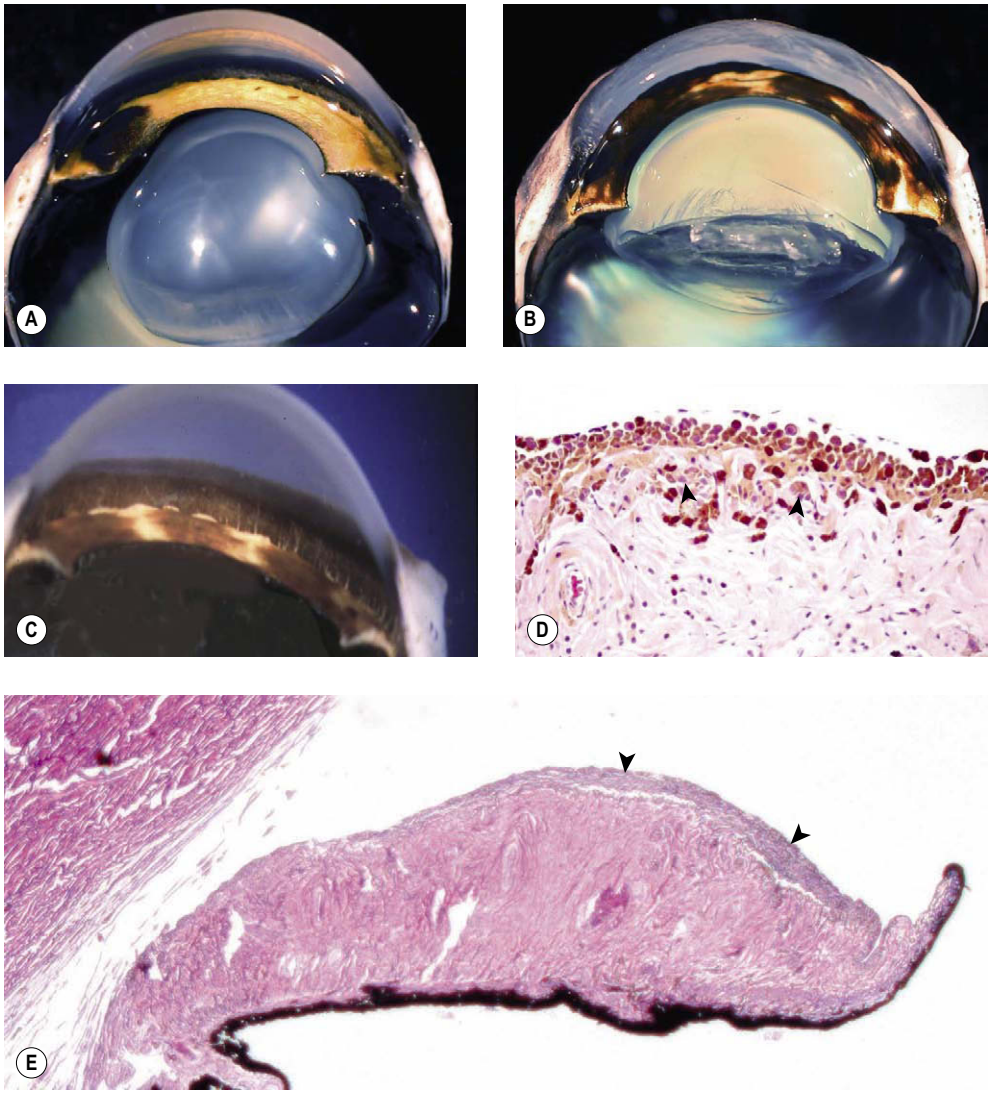


Figure 9.44 Feline iris melanosis and early FDIM. (A–C) Gross photographs showing the early stages of FDIM or, in the case of (A), feline iridal melanosis. (D) Photomicrograph of the anterior surface of the iris showing the earliest stages of FDIM characterized by neoplastic cells extending into the iris stroma (arrows) and not just on the surface. If dysplastic pigment cells are confined to the anterior surface only, that defines feline iridal melanosis. However, these cells extend a short distance into the iris stroma defining early FDIM. (E) Low magnification photomicrograph of a feline iris in which the pigmented cells are only on the surface (arrows), therefore, melanosis.

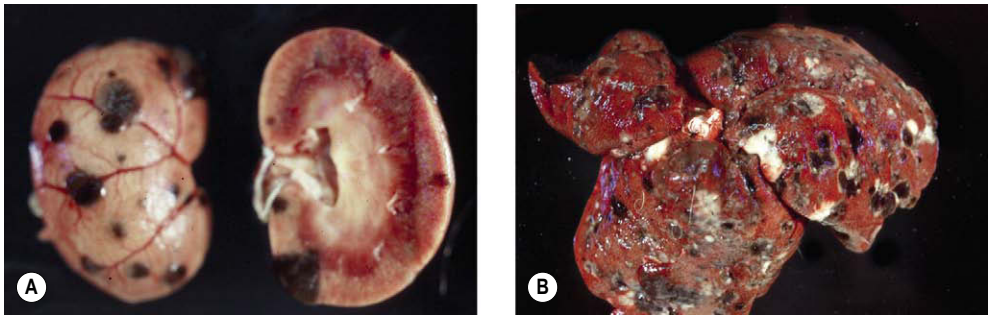


Figure 9.45 Metastatic FDIM. (A,B) Metastatic FDIM in the kidney and the liver. Metastatic disease, when it occurs, is most likely to occur in the abdominal cavity.

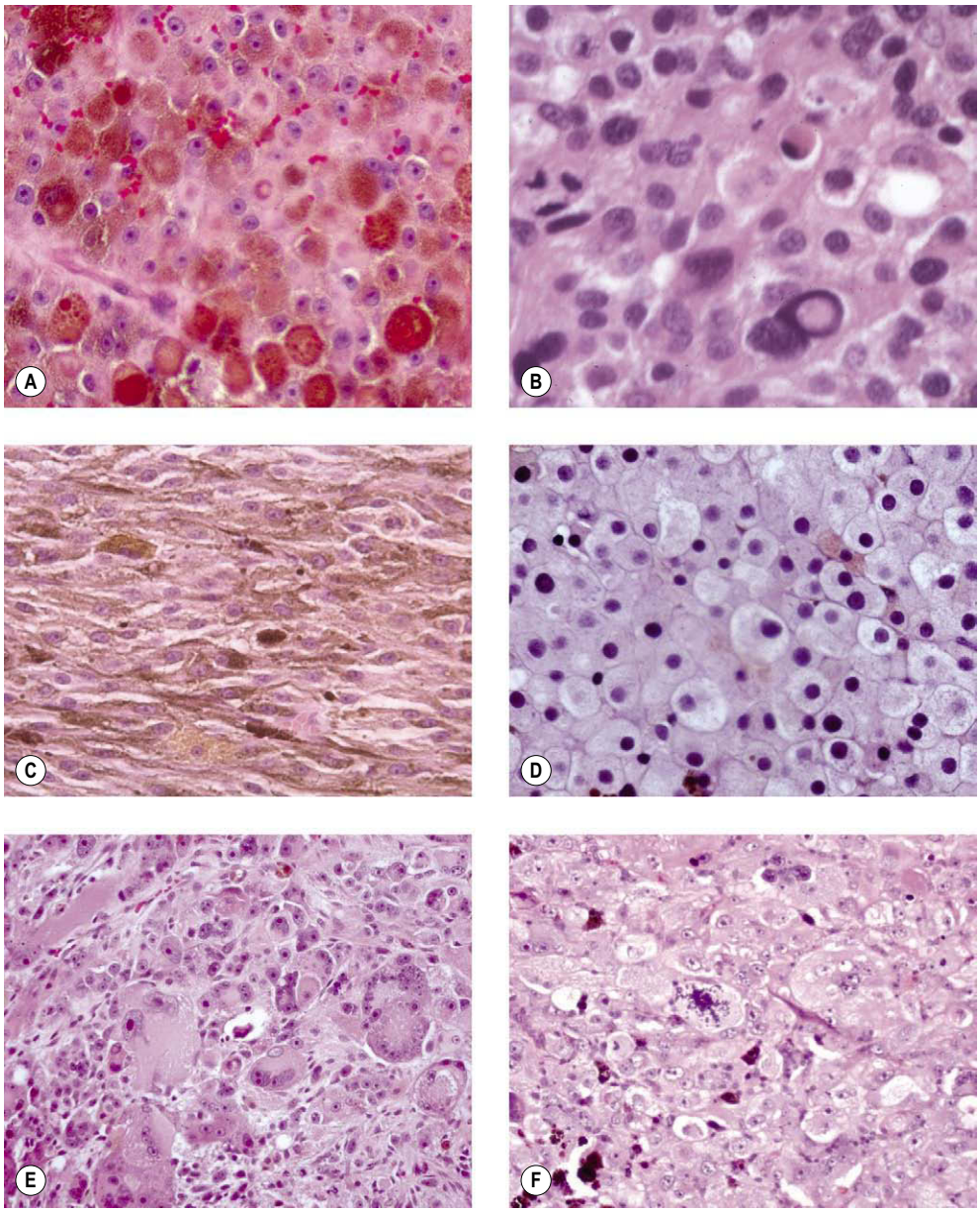


Figure 9.46 FDIM, microscopic. The montage illustrates some of the histologic variability in feline diffuse iris melanoma. (A,B) Examples of round and polygonal cell tumors, the most common types. (C) Spindle cells. (D) Balloon cells, common as individual cells or in small clusters, and, more rarely, as whole populations of cells. (E,F) Anaplastic tumors with multinucleate forms.

Uveal epithelial tumors

Irido-ciliary epithelial tumors in dogs (Figs 9.48, 9.49)

There are 718 cases in the COPLOW collection, accounting for 12.5% of canine neoplastic submissions

- Tumors of the irido-ciliary epithelium are the second most common primary ocular neoplasm in dogs
- The signalment of affected dogs represented in the COPLOW collection may be summarized as follows:
  - The average age of affected dogs is 8.2 years
  - Affected dogs by gender (where known):
    - Males: 83
    - Neutered males: 274
    - Females: 34
    - Spayed females: 288
  - There are 113 Golden Retrievers and 165 Labrador Retrievers, with this breed accounting for 39% of cases
- Irido-ciliary epithelial tumors can arise from either the non-pigmented or pigmented epithelium of the ciliary body or, less frequently, the iris
- Irido-ciliary epithelial tumors often present because of a pink, tan or pigmented mass in the posterior chamber or anterior chamber
- The main differential considerations are melanocytoma and malignant melanoma
- Clinical diagnosis may be complicated in cases with corneal opacity, intraocular hemorrhage, or other opacity of the ocular media
- Other conditions that are frequently associated or concurrent with irido-ciliary epithelial tumors include:
  - Neovascular glaucoma
  - Intraocular hemorrhage
  - Asteroid hyalosis, although generally considered to be of little clinical significance, is seen in association with 27% of canine irido-ciliary epithelial tumors

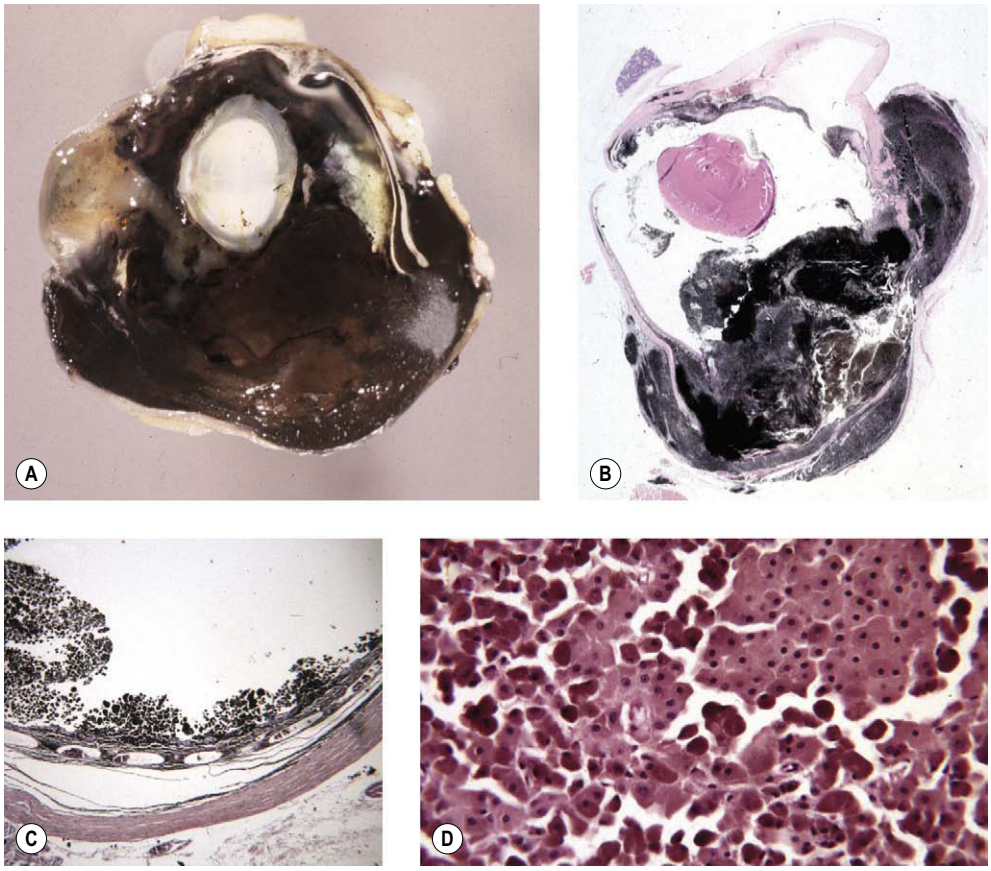


Figure 9.47 Feline atypical uveal melanoma. (A) Gross photograph showing atypical ocular melanoma in a cat. The tumor is darkly pigmented and multifocal. (B) Subgross photomicrograph of feline atypical ocular melanoma showing extensive and multifocal involvement with extension well beyond the sclera. (C) Low magnification photomicrograph showing the characteristic involvement of the RPE in feline atypical ocular melanoma. (D) Photomicrograph of a bleached section showing the characteristic bland tumor cells with a round profile and bland-appearing round nuclei.

- Classification based on invasiveness (Fig. 9.50)
  - Non-invasive adenoma
    - These tumors are entirely confined to the posterior or anterior chamber and do not invade the substance of the uvea
  - Uveo-invasive adenoma
    - These tumors are still considered benign by morphologic criteria. Although they invade the uveal stroma they do not demonstrate scleral invasion
  - Irido-ciliary adenocarcinoma
    - Tumors which invade the sclera are designated adenocarcinoma by virtue of their invasive behavior; 116 cases in the COPLOW collection are classified as adenocarcinoma based on these criteria
    - Adenocarcinoma has a more anaplastic morphologic phenotype than adenoma but is still not likely to metastasize
    - The more aggressive and infiltrative the tumor, the more likely the neoplastic cells are to be positively immuno-labelled for cytokeratin as well as vimentin
  - Pleomorphic adenocarcinoma (Fig. 9.51)
    - Very rarely, adenocarcinoma of the irido-ciliary epithelium is aggressively invasive, extending throughout the globe and infiltrating deeply into the orbit and into vascular structures
    - There are 10 cases in the COPLOW collection and all of them are in eyes with a history of chronic disease, diagnosed as uveitis or glaucoma
    - These tumors resemble the extremely rare human tumor, pleomorphic adenocarcinoma and they are likely to metastasize
    - Usually stain with both cytokeratin and vimentin
- Morphologic features of canine irido-ciliary epithelial tumors (Fig. 9.52)
  - Morphologic features of the epithelial cells
    - 90% of the neoplasms are predominantly non-pigmented, although about half of the tumors have some pigmented cells
    - Degree of differentiation varies with biologic behavior
    - Morphologic variants are:
      - Palisading ribbons, the most common pattern
      - Pleomorphic solid sheets
      - Anaplastic
  - Morphologic patterns of the extracellular matrix
    - 60% of these neoplasms demonstrate thick, branching basal laminae, in a very distinctive pattern, which stain magenta with PAS stain in at least a portion of the tumor
    - The remainder have thin basal laminae which subdivide cords, clusters, or sheets of neoplastic cells
  - Many exhibit extracellular hyaluronic acid secretion
    - This can be demonstrated by Alcian blue staining, before and after treatment of tissue sections with hyaluronidase
  - Extracellular metaplastic bone is seen only rarely in canine tumors

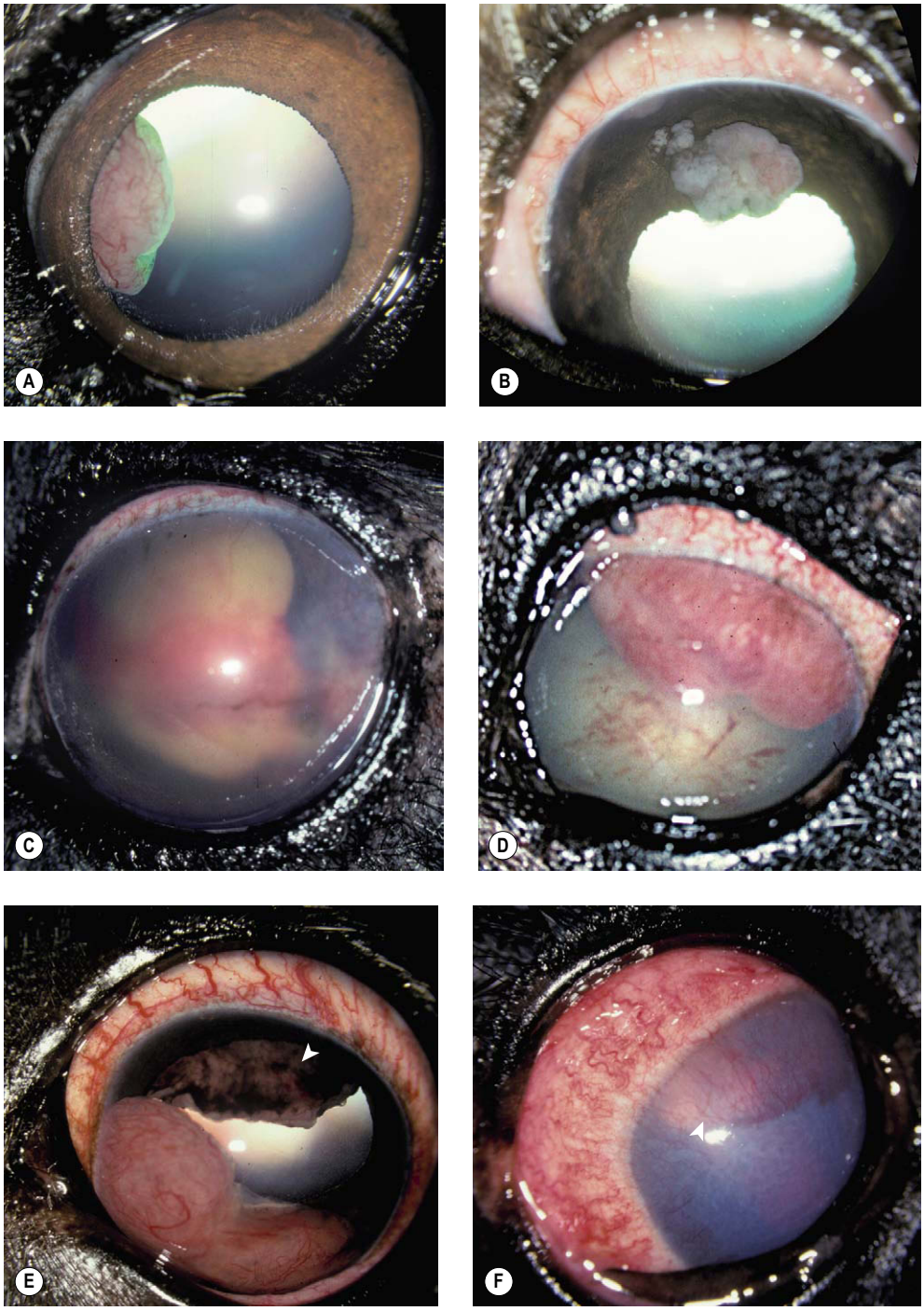


Figure 9.48 Canine irido-ciliary epithelial tumors, clinical. (A) Japanese Akita, 8 years old: a pink vascularized ciliary body adenoma is present. (B) Beagle, 10 years old: the white cauliflowered mass was diagnosed as an irido-ciliary adenoma. (C) Mixed Breed, 8 years old: the anterior chamber is filled with a yellow-pink mass with hemorrhage. This was diagnosed as a ciliary body adenocarcinoma. (D) Poodle, 10 years old: the ciliary body adenocarcinoma totally occluded the angle superiorly. Strands of hemorrhage are present on the corneal endothelium. (E) Boston Terrier, 6 years old: both the apigmented mass inferiorly and the pigmented mass (arrow) arising from the posterior iris were diagnosed as a ciliary body adenoma. (F) Cocker Spaniel, 12 years old: detail of the anterior segment is concealed due to the corneal edema and vascularization. The ciliary body adenoma can be seen adjacent to the cornea (arrow).

- Immunohistochemical profile:
  - Vimentin positive
  - Neuron specific enolase positive
  - S-100 labelling is variable
  - Cytokeratin labelling variable
    - Benign irido-ciliary adenomas are often cytokeratin negative
    - Overall, cytokeratin expression appears to increase with increasing aggressiveness of the neoplasm
    - Cytokeratin 20 expression appears to decrease with increasing aggressiveness of the neoplasm
  - TERT (telomerase reverse transcriptase) staining increases with increasing aggressiveness of the neoplasm
- Pathologic features often seen in association with canine irido-ciliary epithelial tumors include: (Fig. 9.53)
  - Pre-iridal fibrovascular membranes (PIFVM)
    - These can be associated with intraocular hemorrhage and/or neovascular glaucoma
  - Asteroid hyalosis
    - 27% of dogs with irido-ciliary epithelial tumors also have asteroid hyalosis.

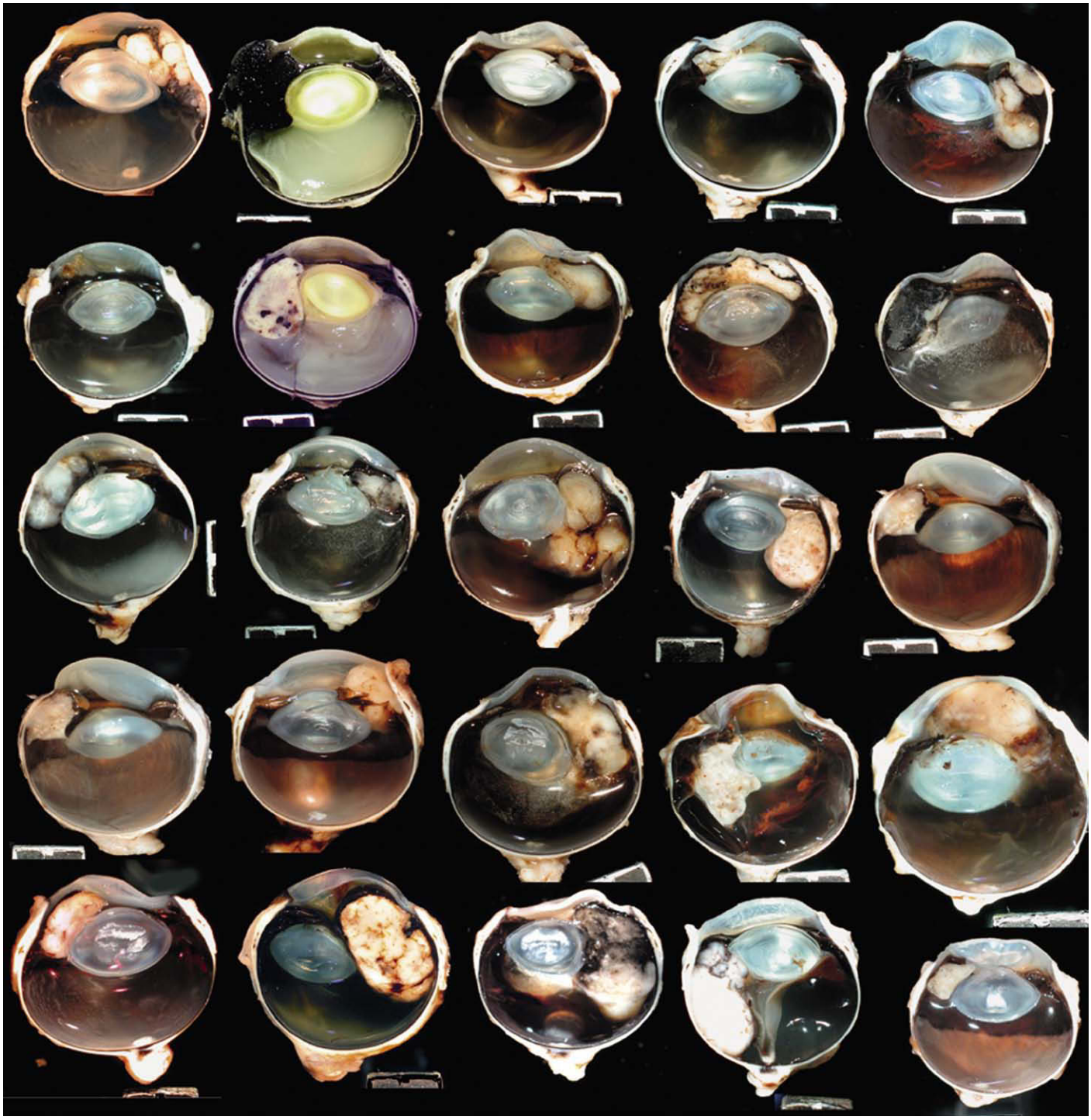


Figure 9.49 Canine irido-ciliary epithelial tumors, gross pathology. A montage of 25 dog eyes showing the variations in the gross appearance of irido-ciliary epithelial tumors. The characteristic feature is to fill the posterior chamber and cradle the lens. The tumors can be pigmented or non-pigmented.

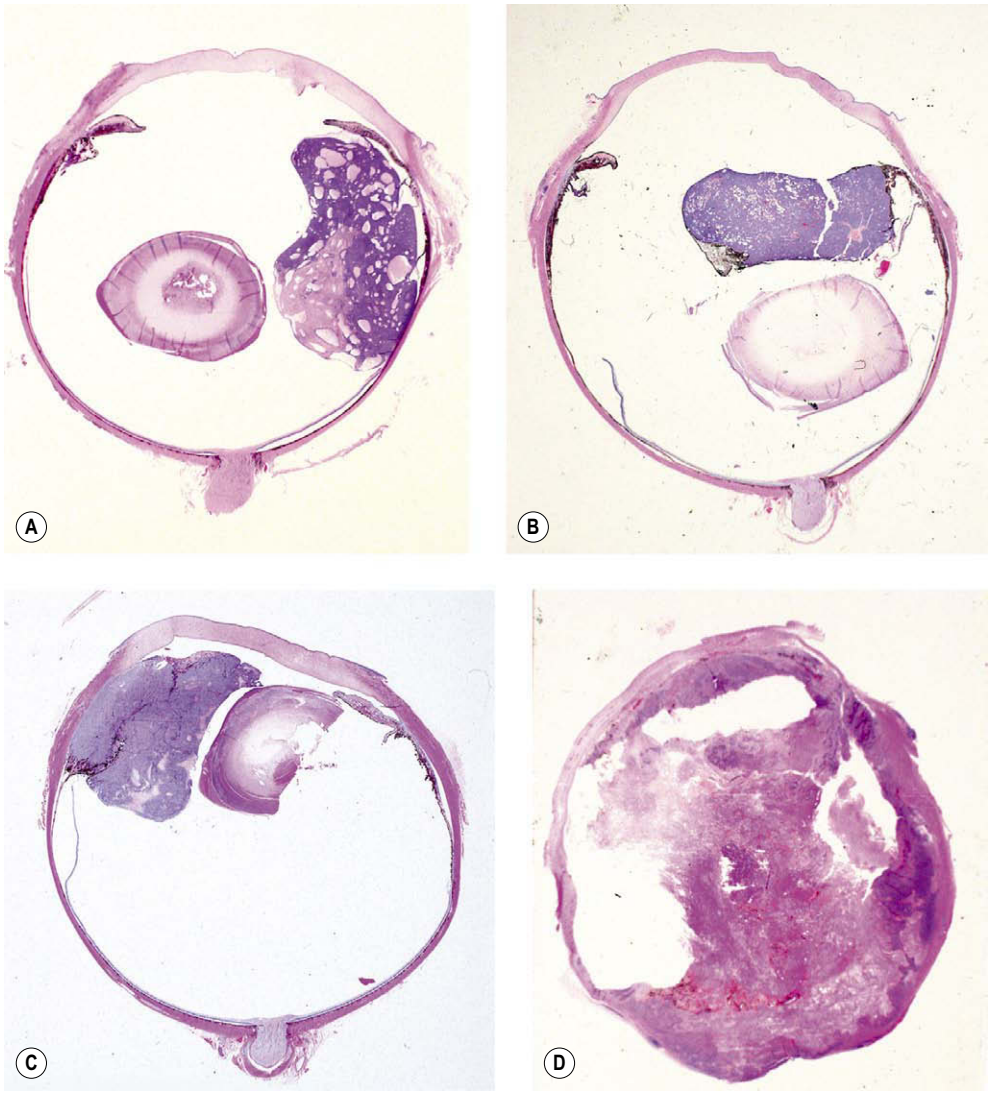


Figure 9.50 Canine irido-ciliary epithelial tumors, invasiveness. (A) Subgross photomicrograph showing canine irido-ciliary tumor, which is not invading the uveal tract and exists entirely within the aqueous-filled posterior chamber. (B) Subgross photomicrograph showing an uveoinvasive tumor. (C) Subgross photomicrograph showing an adenocarcinoma, a tumor that invades both the uvea and the inner sclera. (D) A truly malignant canine irido-ciliary adenocarcinoma with features of the human pleomorphic adenocarcinoma.

Irido-ciliary epithelial tumors in cats

There are 103 cases of irido-ciliary epithelial tumors in cats (Figs 9.54, 9.55) in the COPLOW collection. Together, these constitute 2% of the feline submissions and 3.7% of feline ocular neoplasms.

- Irido-ciliary epithelial tumors are the fourth most common intraocular neoplasm in cats, following diffuse iris melanoma, lymphoma and post-traumatic sarcoma
- The signalment of affected cats may be summarized as follows:
  - The average age of affected cats is 9.1 years
  - Affected cats by gender (where known)
    - Males: 6
    - Neutered males: 45
    - Females: 1
    - Spayed females: 39
- Feline irido-ciliary epithelial tumors generally fill the posterior chamber, cradle the lens equator, and infiltrate the iris, ciliary body, anterior chamber, and rarely the inner sclera
- Morphologic features of feline irido-ciliary epithelial tumors: (Fig. 9.56)
  - These tumors are almost always composed of non-pigmented epithelial cells
  - They seldom contain cords or ribbons of epithelial cells; rather, they are composed of solid sheets of polygonal cells which can be difficult to recognize as being epithelial
  - There is a delicate but very regular vascular stroma which subtly subdivides the tumor mass into small subunits, and is made more apparent with the PAS stain
  - About 30% of feline irido-ciliary adenomas have metaplastic bone within the mass
  - The solid sheets of tumor tissue are often interrupted by cavitated cystic spaces. Occasionally, the tumors are predominantly cystic.

Feline ocular neuroglial tumor (Fig. 9.57)

This is a rare but distinctive neoplasm arising in the uvea of cats. There are four cases in the COPLOW collection.

Morphologic features

- The tumor appears solid and white on observation at the time of gross sectioning
- The tumor bulges inward, extending from the uveal tract

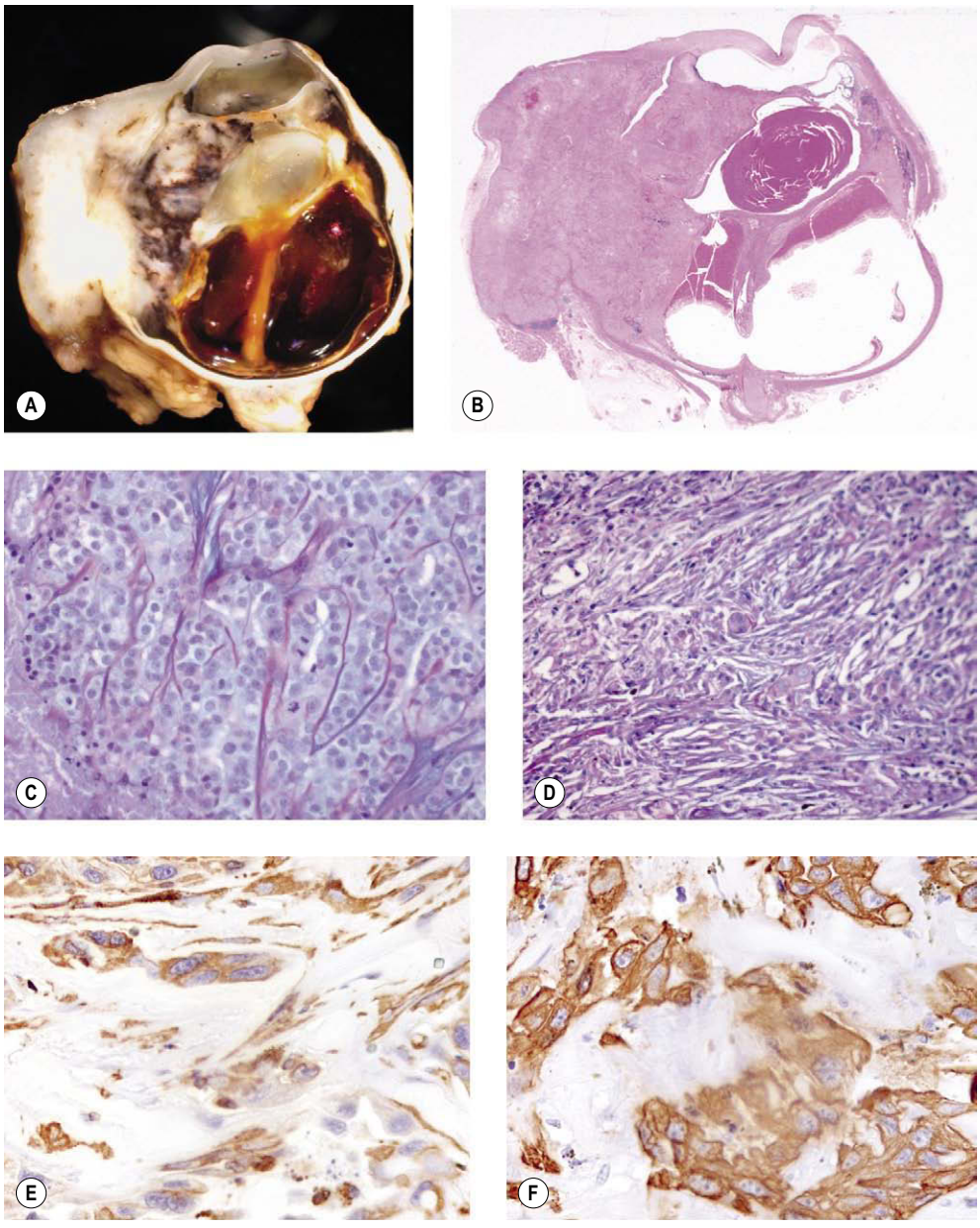


Figure 9.51 Canine irido-ciliary adenocarcinoma (pleomorphic adenocarcinoma). (A) Gross photograph of a highly malignant canine irido-ciliary adenocarcinoma (pleomorphic adenocarcinoma). (B) Subgross photomicrograph of the globe in (A). (C,D) Photomicrographs showing the histologic appearance of pleomorphic adenocarcinoma using a PAS stain. The distinct sharply delineated basement membrane is often very regionally apparent. (E) Immunohistochemical stain for vimentin showing the characteristic positive staining. (F) Positive staining for cytokeratin, a feature seen more often in malignant tumors of irido-ciliary origin and less commonly in benign tumors.

- Histologically, the tumor is a spindle cell tumor with moderately anaplastic features
- Immunohistochemical profile
  - Melan A negative (an antigen expressed by melanocytes)
  - GFAP positive (a marker for glial cells)
  - S100 positive (indicative of a neural crest derivation)
  - Synaptophysin positive (a protein associated with synaptic transmission and neuroendocrine function)
  - Chromogranin A positive (a neuroendocrine secretory protein)
  - Desmin positive (indicating muscle tissue differentiation)
  - Skeletal muscle actin positive (a skeletal muscle isoform of actin)
- The immunohistochemical profile suggests a neoplasm with neural, glial, and skeletal muscle features
  - Skeletal muscle is a feature of teratoid medulloepithelioma in humans, however these feline tumors lack other features characteristic of medulloepithelioma.

Medulloepithelioma (Figs 9.58, 9.59)

- Medulloepithelioma is an ocular neoplasm in the general family of primitive neuroectodermal tumors (PNET)
  - These tumors arise from different tissues that are derived from primitive neuroectoderm of the neural tube
  - On the one hand, medulloepithelioma is closely related to irido-ciliary adenoma and on the other hand, the tumor shares many features with retinoblastoma (discussed in further detail in Ch. 11)

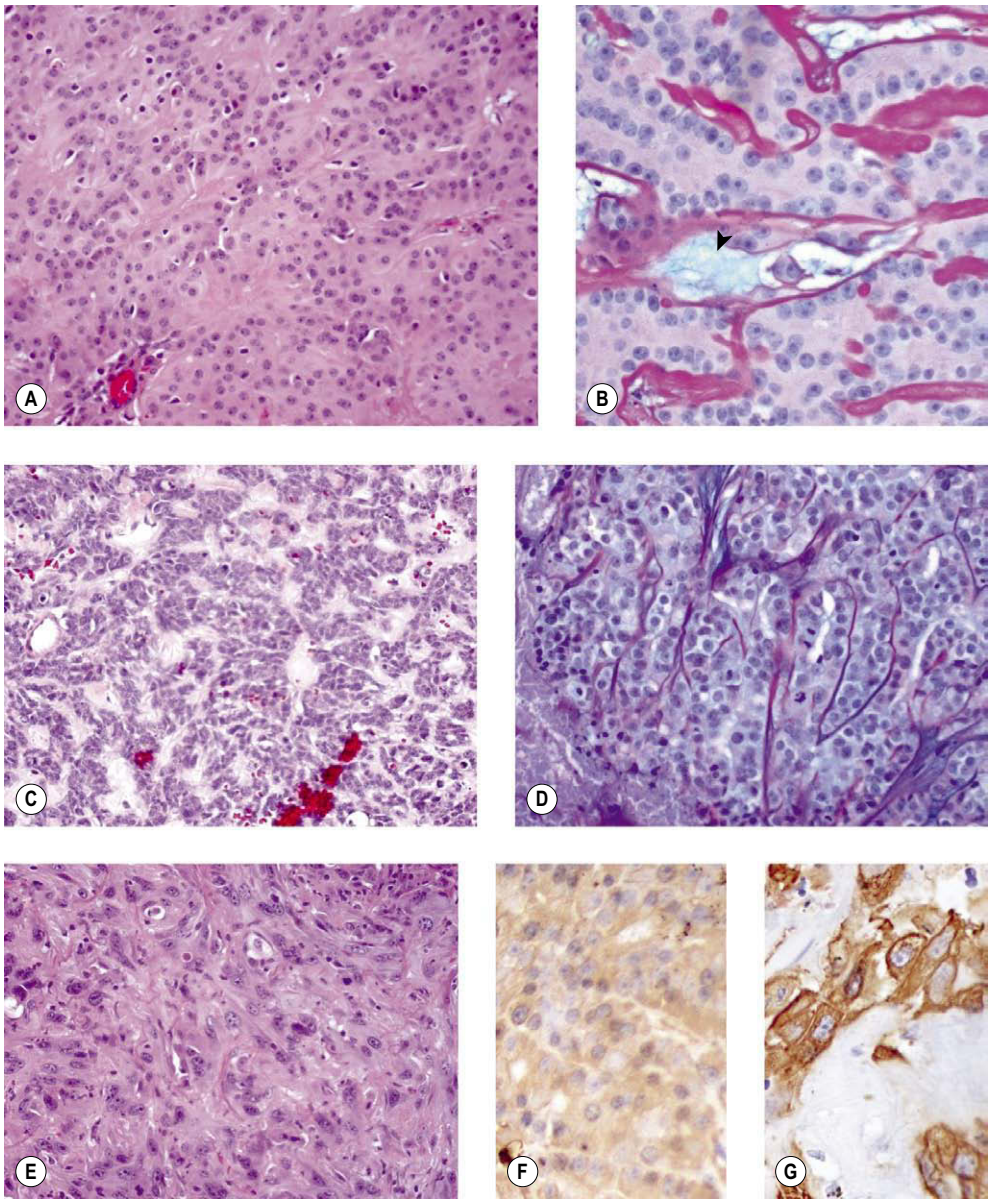


Figure 9.52 Canine irido-ciliary epithelial tumors, microscopic. (A) Photomicrograph showing the most typical features seen in canine irido-ciliary adenoma. Bland epithelial cells are arranged along thick but indistinct eosinophilic basement membrane structures (H&E). (B) Photomicrograph of an Alcian blue PAS-stained specimen from an area similar to (A). With PAS, the basement membranes stand out. The Alcian blue-positive extracellular hyaluronic acid is also characteristic (arrow). (C) Photomicrograph showing less-differentiated epithelial features in a case without the thick basement membranes. (D) PAS-stained tumor with thinner basement membranes than (B) and more cellular atypia than (A) or (B). (E) Irido-ciliary epithelial tumor with anaplastic cellular features including multinucleate cells. (F) Immunohistochemical stain for vimentin showing characteristic positive staining. Both benign and malignant tumors stain with vimentin, as does the native irido-ciliary epithelium. (G) Immunohistochemical stain for cytokeratin is positive, which is characteristic of the more anaplastic or invasive tumors. The benign tumors and the native irido-ciliary epithelial cells do not stain with broad-spectrum cytokeratin.

  - Retinoblastoma is a common retinal neoplasm of humans but is exceedingly rare in domestic animals
  - Irido-ciliary adenoma in dogs can have features typical of medulloepithelioma in segments of the tumor
- Medulloepithelioma is a very rare tumor in dogs and horses, and is extremely rare in cats
  - There are 29 cases in the COPLOW collection:
    - 24 in dogs
    - 2 in horses
    - 1 in a cat
    - 2 in other species (llama and goldfish)
  - Isolated cases have been reported in other species, including birds and llama. However, reports are too sparse to allow an estimate of the prevalence of this neoplasm
- Medulloepithelioma often occurs in young animals but there are many exceptions:
  - For example, only 7 of the 24 canine in cases in the COPLOW archive are from dogs less then 5 years old
- In dogs, the tumors usually originate in the ciliary body and can extend to involve the retina, whereas in horses some of the tumors originate in the optic nerve
- Morphologic features of medulloepithelioma:
  - The tumors are delicate, often multiple white masses, often within the posterior chamber, and they can be locally infiltrative
  - Tumors often have papillary or botryoid extensions within the aqueous humor and, in some cases, can seed the anterior chamber with miliary, small nodular metastatic foci
  - Tumors tend to show a pattern of survival around blood vessels with extensive necrosis away from vessels
  - The hallmark histological feature is the formation of rosettes
    - Flexner–Wintersteiner rosettes and Homer–Wright rosettes are also seen in retinoblastoma and other PNET Tumors and are not specific for medulloepitheliomas

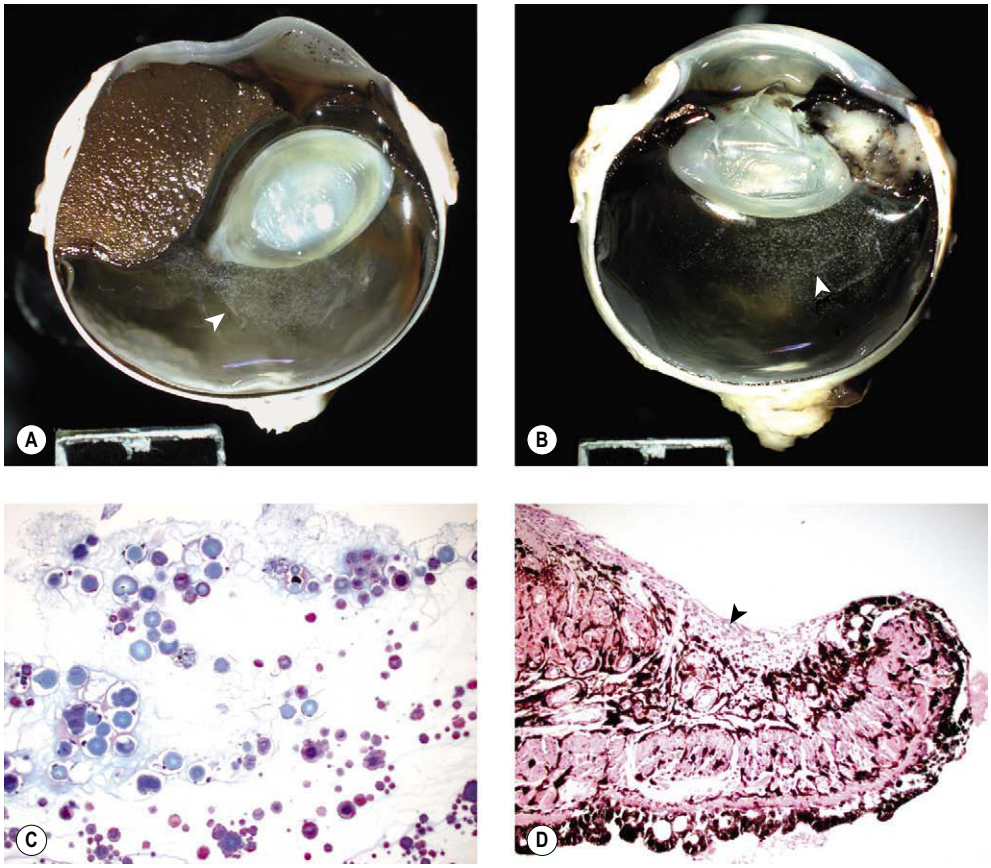


Figure 9.53 Secondary features associated with irido-ciliary epithelial tumors. (A) Gross photograph of a canine globe with a pigmented irido-ciliary adenoma and prominent asteroid hyalosis (arrow). (B) Gross photograph of canine globe with irido-ciliary adenoma and asteroid hyalosis (arrow). (C) Photomicrograph showing asteroid hyalosis (Alcian blue PAS). (D) Photomicrograph showing preiridal fibrovascular membrane and ectropion uvea in a canine globe with irido-ciliary epithelial tumor (arrow).

  - Larger, more complex multi-layered rosettes or tube structures lined by columnar neuroblastic cells are the defining feature of medulloepithelioma
- Although medulloepithelioma is locally invasive it is only rarely metastatic.

Comparative Comments

- Tumors of the retinal pigment epithelium and the epithelium of the ciliary body and iris are uncommon in humans and, in general, parallel the description given for other species. These may take the form of adenomas or adenocarcinomas
- Medulloepitheliomas (dictyomas) are congenital neuroepithelial tumors arising from primitive medullary epithelium and are usually located in the ciliary body. Although some of these tumors appear histologically malignant, most have a relatively benign course if confined to the eye
- Fuchs adenomas are benign proliferations of the nonpigmented ciliary epithelium. These are usually an incidental finding at autopsy or enucleation and rarely have clinical significance.

Uveal lymphoma and histiocytic neoplasia

Uveal lymphoma in cats (Fig. 9.60)

There are 284 cases in the COPLOW collection, accounting for 5.5% of feline submissions and 10% of ocular neoplastic submissions in cats

- Uveal lymphoma is the second most common intraocular neoplasm of cats
  - These cases do not include the round cell variant of feline post-traumatic ocular sarcoma (FPTOS). The round cell variant of FPTOS is distinguished from feline uveal lymphoma unrelated to trauma by its wide distribution in the globe, presence of lens capsule rupture, extent of necrosis and history. This tumor, which is also a form of lymphoma, is discussed in greater detail in Chapter 5 and later in this chapter.
- The average age of affected cats is 9.8 years and there is no breed predilection. The FeLV/FIV status of affected cats is not often recorded in the COPLOW archive, however, there is no reason to believe that cats with uveal lymphoma are commonly infected by either retrovirus
- Approximately half of feline uveal lymphomas are seen in combination with lympho-plasmacytic uveitis:
  - The relationship between lymphoma and inflammation is not clear
  - Lymphoma in association with uveitis is less likely to clearly express markers of T-cell or B-cell differentiation. However, these neoplasms are just as likely to impact lifespan/survival
- Based on limited follow-up information available, uveal lymphoma generally represents a systemic rather than localized disease process. However, ocular disease is frequently the presenting complaint and may precede signs of systemic involvement
  - This experience suggests that chemotherapy may be warranted in cats following enucleation of a globe that appears to be affected in isolation

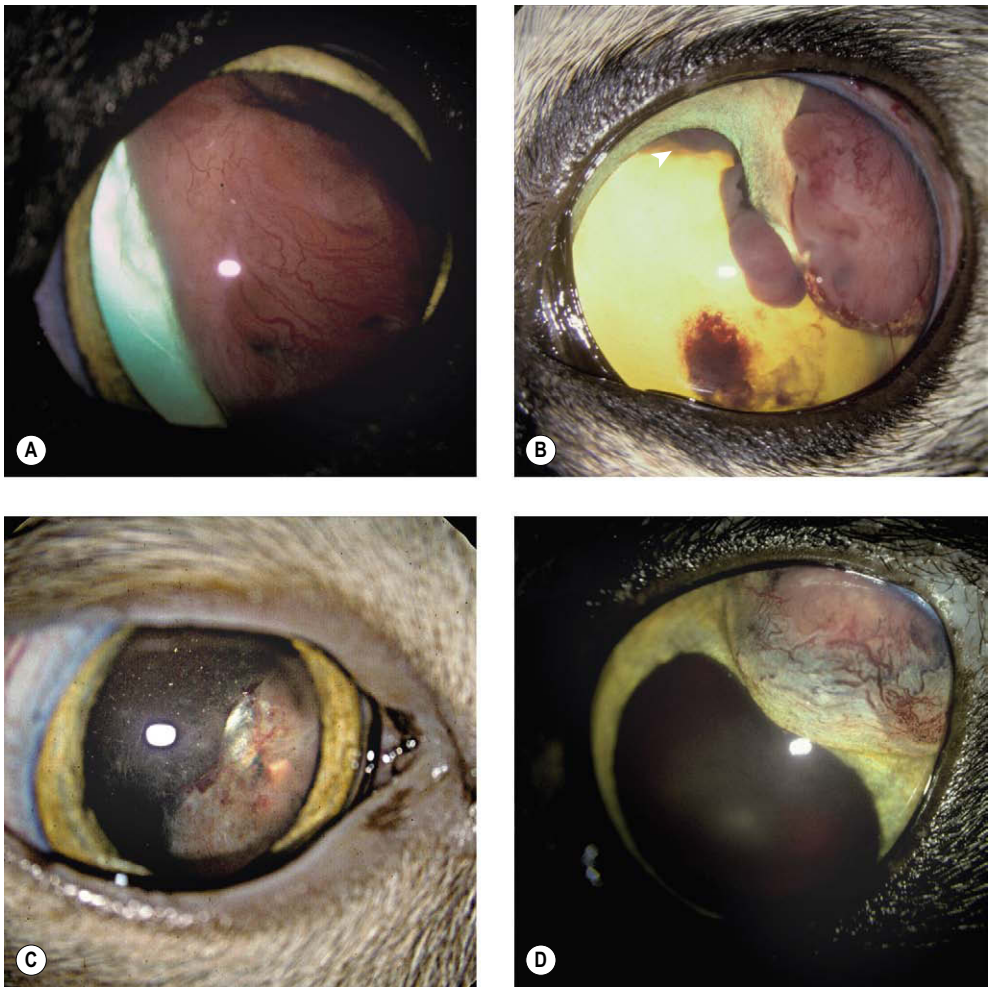


Figure 9.54 Feline irido-ciliary epithelial tumors, clinical. (A) DSH, 7 years old: the large pink vascularized ciliary body adenoma fills almost the entire pupil. (B) DLH, 9 years old: this irido-ciliary adenoma has extended through the angle and into the anterior and posterior chambers (arrow). Resulting hemorrhage is present in the anterior chamber inferiorly. (C) DSH, 9 years old: this irido-ciliary adenoma is extending from the posterior iris. The mass also resulted in a retinal detachment. (D) DMH, 11 years old: the irido-ciliary adenoma has invaded through the angle and into the iris stroma. Extensive vitreous hemorrhage prevented visualization of the fundus.

- The most common ocular tissue to be involved is the anterior uvea (iris and ciliary body). Uveal involvement may be nodular or diffuse. However, the retina, choroid, cornea (particularly the limbal region), adnexa, peripheral nerve tissue or optic nerve may also be affected
- The ciliary body epithelium is often distorted by an infiltrate of neoplastic cells, a feature which may prove useful in making the distinction between lymphoma and melanoma, as melanoma is unlikely to specifically affect the ciliary body epithelium
- Immunohistochemical labeling of leukocyte differentiation antigens and/or melanocytic markers can also help to distinguish between lymphoma and amelanotic melanoma
  - There is not enough information to draw conclusions regarding the significance of immunophenotyping of feline ocular lymphoma. However, tumors of both T-cell and B-cell lineage occur.

Uveal lymphoma in dogs (Fig. 9.61)

- Lymphoma is the third most common intraocular neoplasm in dogs
  - There are 188 cases in the COPLOW collection, representing 1.3% of all canine submissions and 3.3% of canine neoplasms in the collection
  - Ocular involvement is common in dogs with multicentric lymphoma
- Ocular involvement is more likely to be bilateral in dogs than in cats, however bilateral cases are less likely to undergo enucleation
- The anterior uvea is the most common tissue involved but lymphoma can also be recognized in the retina, cornea, adnexa, orbit, optic nerve head, or in peripheral nerve tissue
- As is the case in cats, the ciliary body epithelium is often distorted by an infiltrate of neoplastic cells, a feature which may prove useful in making the distinction between lymphoma and melanoma, as melanoma is unlikely to specifically affect the ciliary body epithelium.

Intravascular lymphoma in dogs, malignant angioendotheliomatosis (Fig. 9.62)

There are six cases of intravascular lymphoma affecting the eye in the COPLOW collection, all in different breeds.

- Intravascular lymphoma is a rare condition, characterized by primary neoplastic proliferation of lymphocytes within the lumen of blood vessels

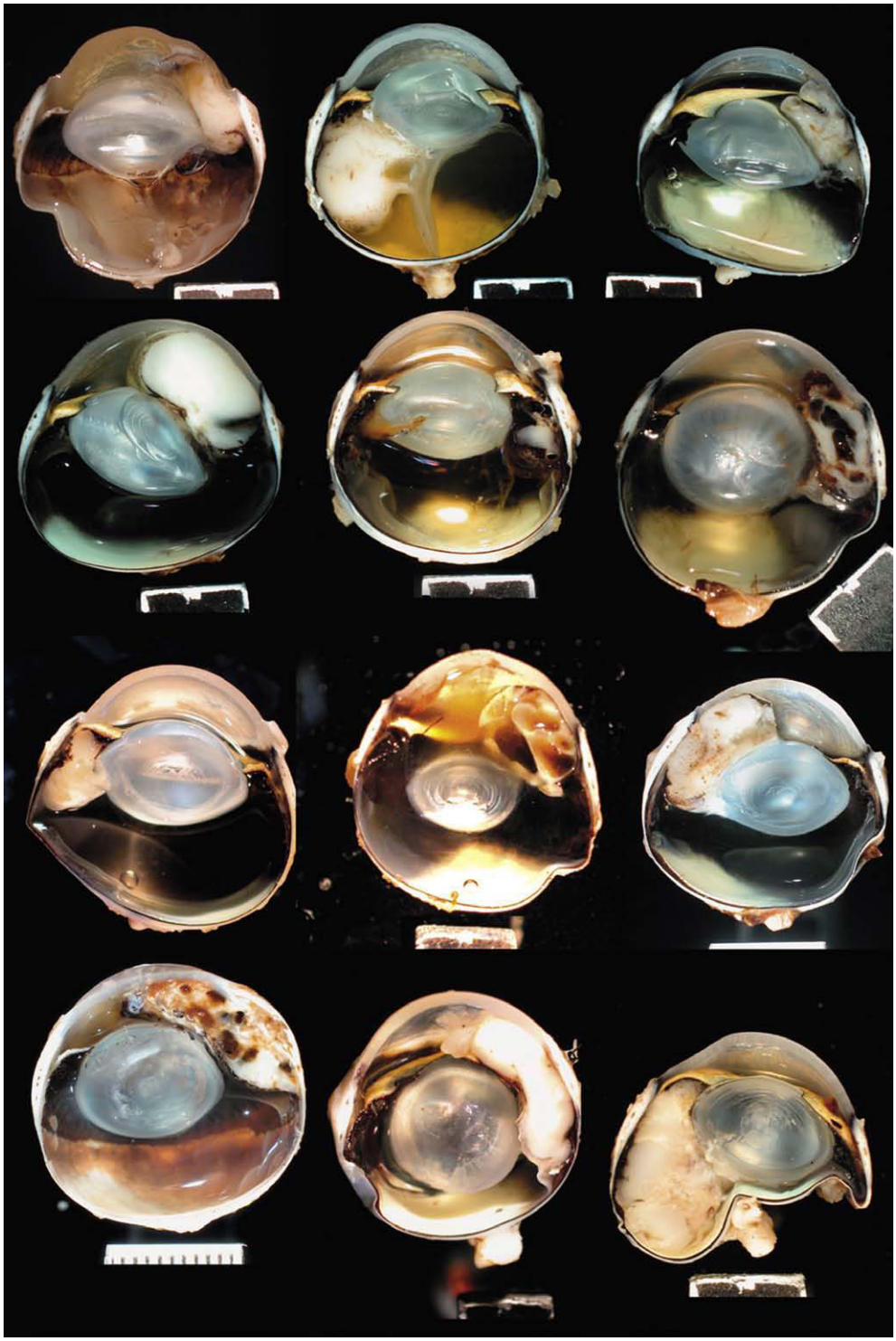


Figure 9.55 Feline irido-ciliary epithelial tumors, gross. A montage of gross photographs of 12 feline globes with irido-ciliary epithelial tumors showing the variations of involvement. The tumors are characteristically white, fill the posterior chamber and cradle the lens.

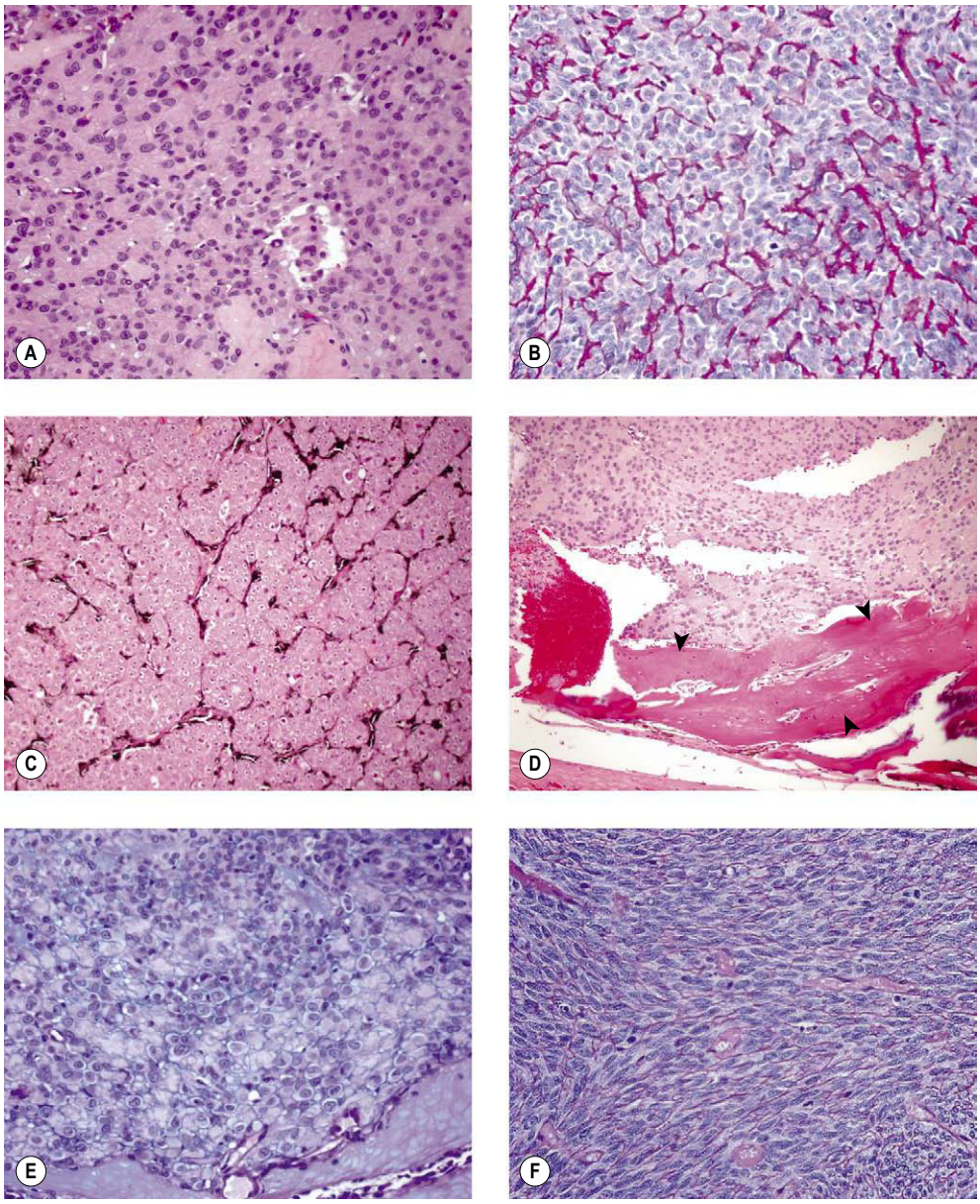


Figure 9.56 Feline irido-ciliary epithelial tumors, microscopic. (A) Photomicrograph showing the typical solid pattern of polygonal cells and scant delicate vascular supply (H&E). (B) The same case as (A) stained with PAS to show the characteristic pattern of thin basement membranes around individual cells or small cell clusters. (C) This case has more obvious epithelial cords and a pigmented background. (D) Photomicrograph showing metaplastic bone (arrows), which is a feature in about half of the feline irido-ciliary epithelial tumors. (E,F) Photomicrographs showing features of two more anaplastic irido-ciliary epithelial tumors. The tumor in (F) is composed of spindle cells.

- The disease is systemic but the eye and the brain are common sites for involvement
  - Clinical signs of ocular disease, including uveitis, panophthalmitis and retinal detachment may precede other signs of systemic involvement
- Morphologic features of intravascular lymphoma
  - Neoplastic lymphocytes fill widely dilated vascular spaces in the uvea
  - Hemorrhage, edema, and infarction are seen in the tissues supplied by the affected vessels.
  - Neoplastic cells can also spill over into the tissues near vessels
  - This neoplasm does not form mass lesions.

Comparative Comments

- Lymphoma of the uveal tract in humans occurs almost exclusively in association with systemic malignant lymphoma
- In addition, the choroid may be involved with lymphoid proliferation, either in association with systemic lymphoproliferative disease or as a primary ocular process
- It is important to distinguish inflammatory pseudotumor from lymphoma on the basis of lymphocyte typing.

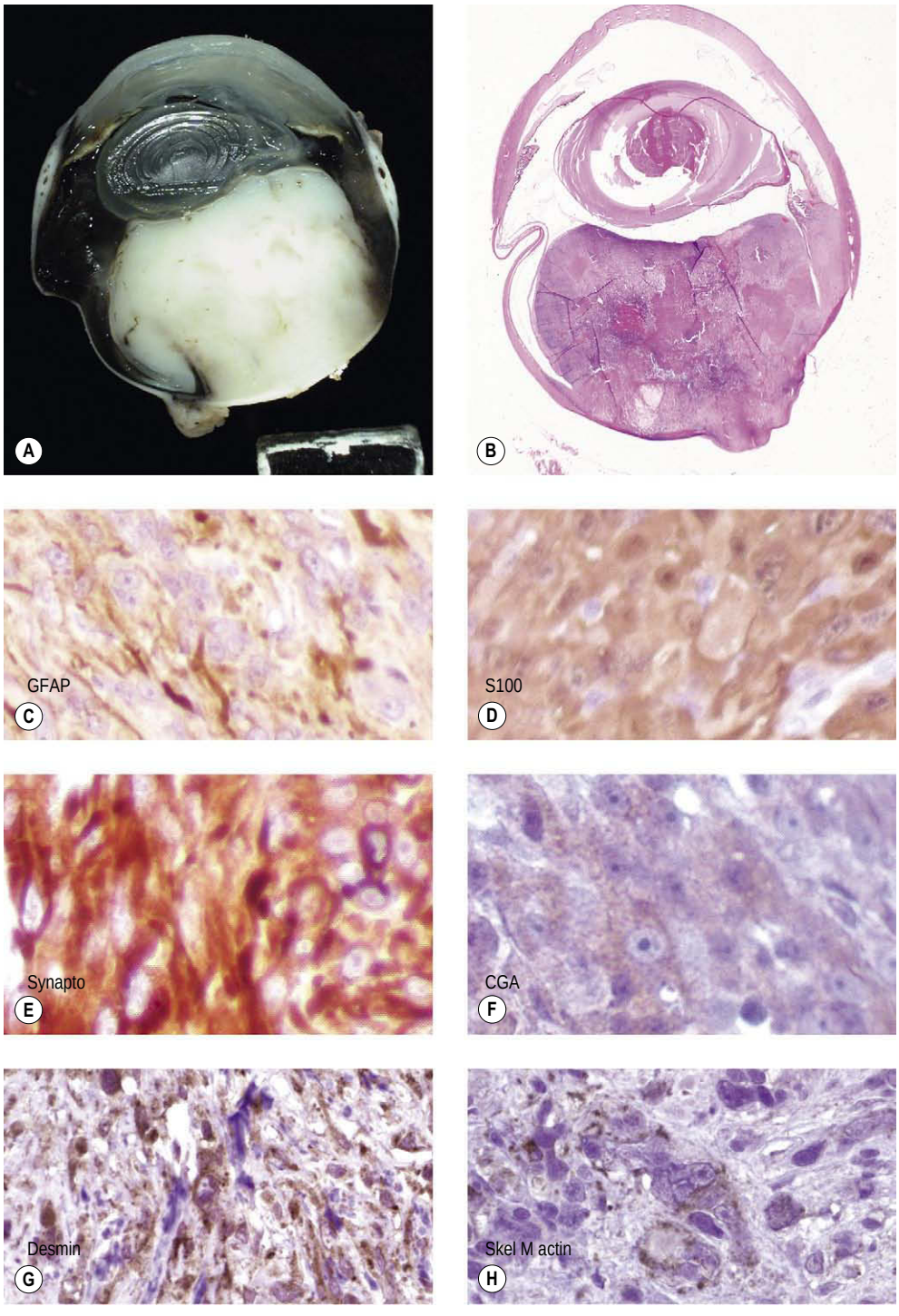


Figure 9.57 Feline ocular neuroglial tumor. (A,B) Gross photograph and subgross photomicrograph showing the characteristic features of feline ocular neuroglial tumor. A solid white tumor extends from the choroid and grows into the center of the globe. (C–H) Immunohistochemical stains showing positive staining for GFAP (C), S-100 (D), synaptophysin (E), chromogranin A (F), desmin (G), and skeletal muscle actin (H).

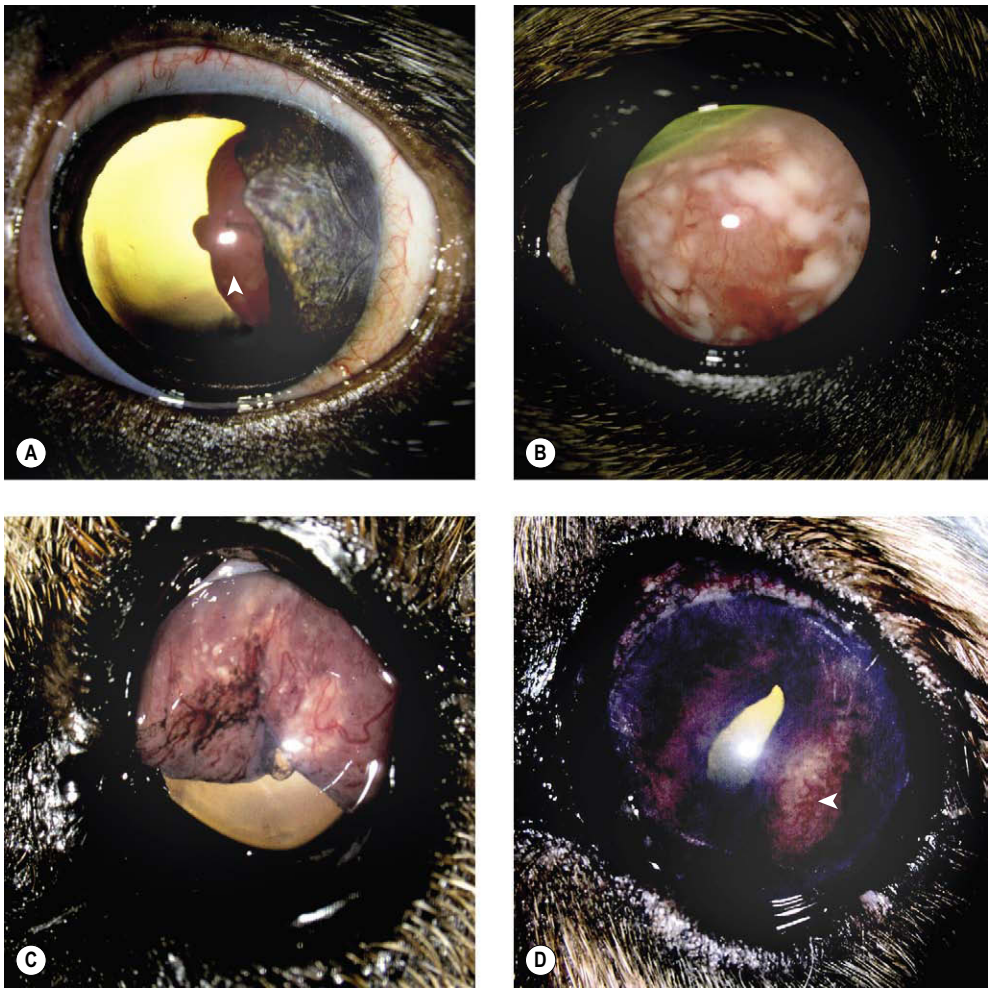


Figure 9.58 Canine medulloepithelioma, clinical. (A) English Springer Spaniel, 2 years old: the whitish pink mass (arrow) has displaced the iris anteriorly. (B) Mixed Breed, 4 years old: a highly vascularized mass fills almost the entire pupil with fluffy white opacities. (C) Chow Chow, 9 years old: this large mass displaced the iris anteriorly. The histological diagnosis was medulloepithelioma or ciliary body adenoma. (D) Cocker Spaniel, 3 years old: the iris is dark and displaced anteriorly. The white mass (arrow) invading the iris added to the dyscoria.

Histiocytic sarcoma and related tumors (Figs 9.63, 9.64)

- Histiocytic sarcoma is a systemic canine neoplasm, in which ocular disease may represent the initial presentation
  - Ocular involvement is typically unilateral
  - The presenting signs frequently relate to uveitis, secondary glaucoma and/or the presence of an intraocular mass lesion
- There are 54 cases in the COPLOW collection with a diagnosis of ocular histiocytic sarcoma
  - In these cases, ocular disease was the initial presentation
- This neoplasm has a strong breed-association. Of the 54 cases in the COPLOW archive:
  - 16 are Rottweilers
  - 18 are Labrador Retrievers
  - 20 are Golden Retrievers
- Affected dogs often have other detectable masses or systemic signs that may be noted at the time of enucleation, or upon subsequent evaluation after histologic diagnosis of the ocular neoplasm
- Life expectancy following diagnosis is very short
- Morphologic features of histiocytic sarcoma include:
  - A solid white mass segmentally effacing uveal tissue
  - Neoplastic cells are pleomorphic, round or polygonal with abundant eosinophilic cytoplasm, cytoplasmic vacuoles, and multinucleate forms
  - Positive by immunohistochemistry for CD18
- Rarer than histiocytic sarcoma is systemic histiocytosis (Fig. 9.65)
  - There are 19 cases of canine systemic histiocytosis in the COPLOW collection
  - Four are in Bernese Mountain dogs
  - Ocular involvement is more likely to be episcleral or orbital than uveal
  - Characterized by a more bland population of histiocytes, often with a vasocentric growth pattern

Spindle cell tumors of the iris in blue-eyed dogs (SCTBED) (Fig. 9.66)

- There are 43 cases of spindle cell tumor of blue-eyed dogs in the COPLOW collection.
  - This is a rare tumor type, accounting for only 0.7% of canine neoplastic submissions in the COPLOW collection
- All affected globes, to date, have had a blue iris or, at least, a partly blue (heterochromic) iris

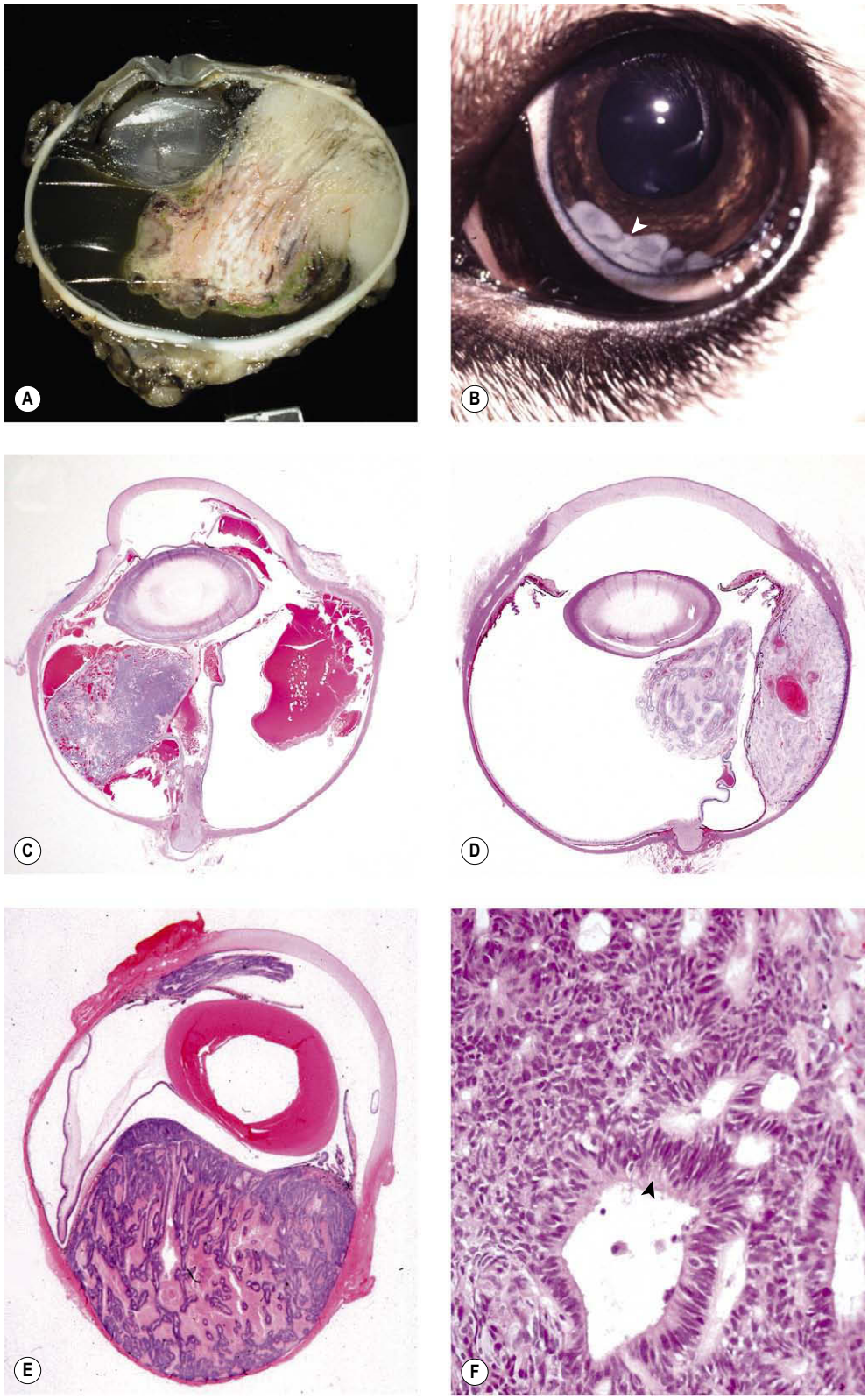


Figure 9.59 Canine medulloepithelioma, pathology. (A) Gross photograph showing a solid white medulloepithelioma filling approximately 60% of a dog's globe. (B) Clinical photograph of a dog eye with medulloepithelioma showing cavitated white tubes of neoplastic tissue in the anterior chamber (arrow). (C–E) Subgross photomicrographic images show medulloepithelioma in three dogs. (F) Photomicrograph showing the characteristic feature of cavitated tubes lined by a complex layer of elongated epithelial cells (arrow).

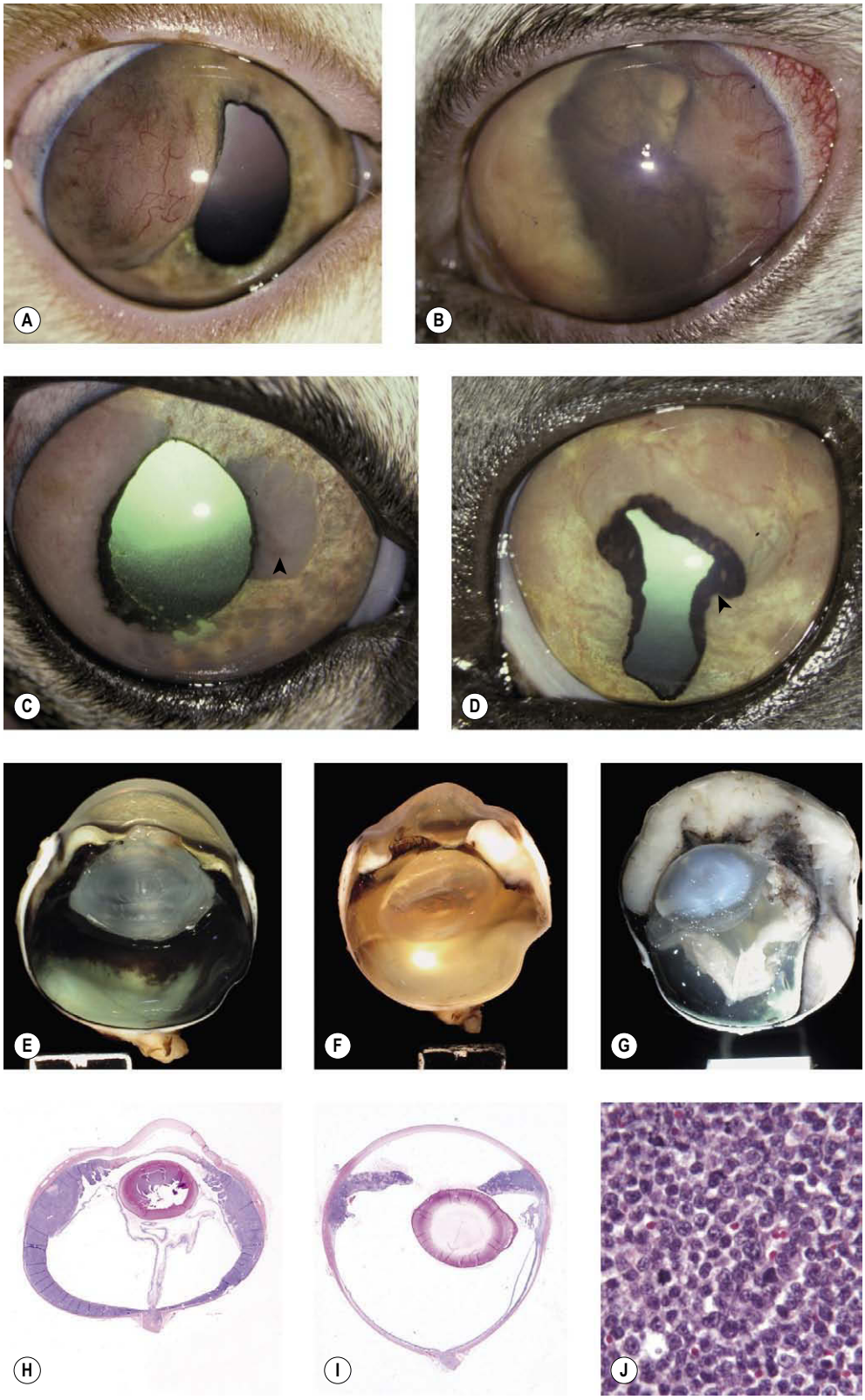


Figure 9.60 Feline uveal lymphoma. (A) DSH, 11 years old: the temporal half of the iris is infiltrated resulting in dyscoria and a shallow anterior chamber. (B) DSH, 13 years old: the entire iris is infiltrated resulting in a posterior synechia and a fibrinous exudate in the anterior chamber. (C) DSH, 12 years old: the smooth pink elevation extends to the pupil margin temporally and nasally (arrow). (D) DSH, 8 years old: the generalized infiltrate in the iris has resulted in a severe dyscoria and in ectropion uvea (arrow). (E–G) Gross photographs showing the typical appearance of solid anterior uveal lymphoma. (H, I) Subgross photomicrographs showing solid uveal neoplastic infiltrates. The case in (H) involves the entire uvea. (J) Photomicrograph showing a monotonous population of neoplastic lymphocytes.

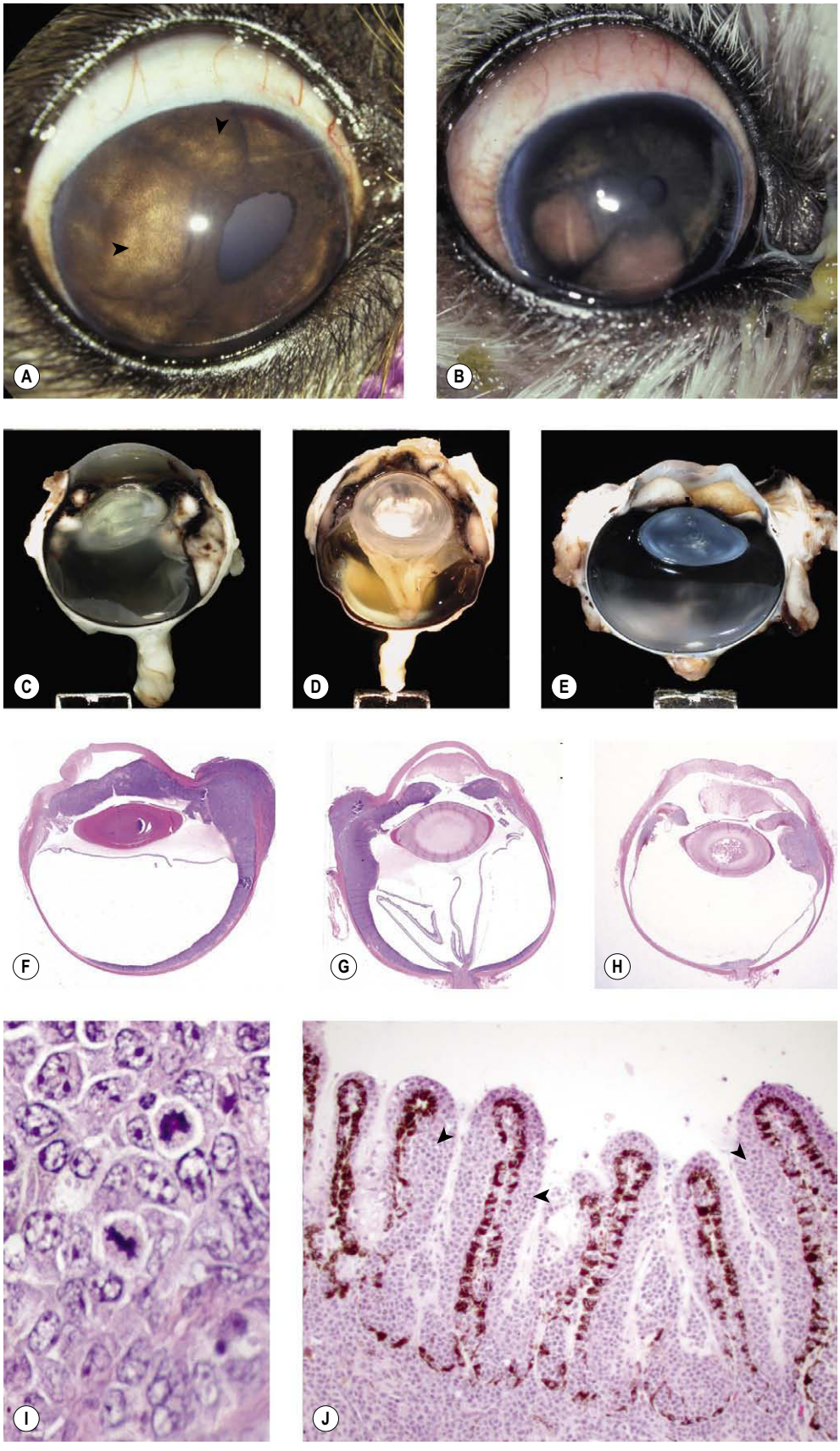


Figure 9.61 Canine uveal lymphoma. (A) Border Collie, 6 years old: nodular elevations of the iris (arrows) were present in both eyes with little aqueous flare. (B) Samoyed, 6 months old: two pink iris nodules are present. The miotic pupil is difficult to observe. (C–E) Gross photographs of canine globes showing the typical pattern of segmental invasion of the anterior uvea with lymphoma. (F–H) Subgross photomicrographs of canine globes showing segmental uveal infiltration by lymphoma. (I) High magnification photomicrograph showing anaplastic-appearing neoplastic lymphocytes in canine lymphoma affecting the eye. (J) Photomicrograph showing tumor in the ciliary body epithelium (arrows), a common finding in lymphoma, but rarely seen in other tumors.

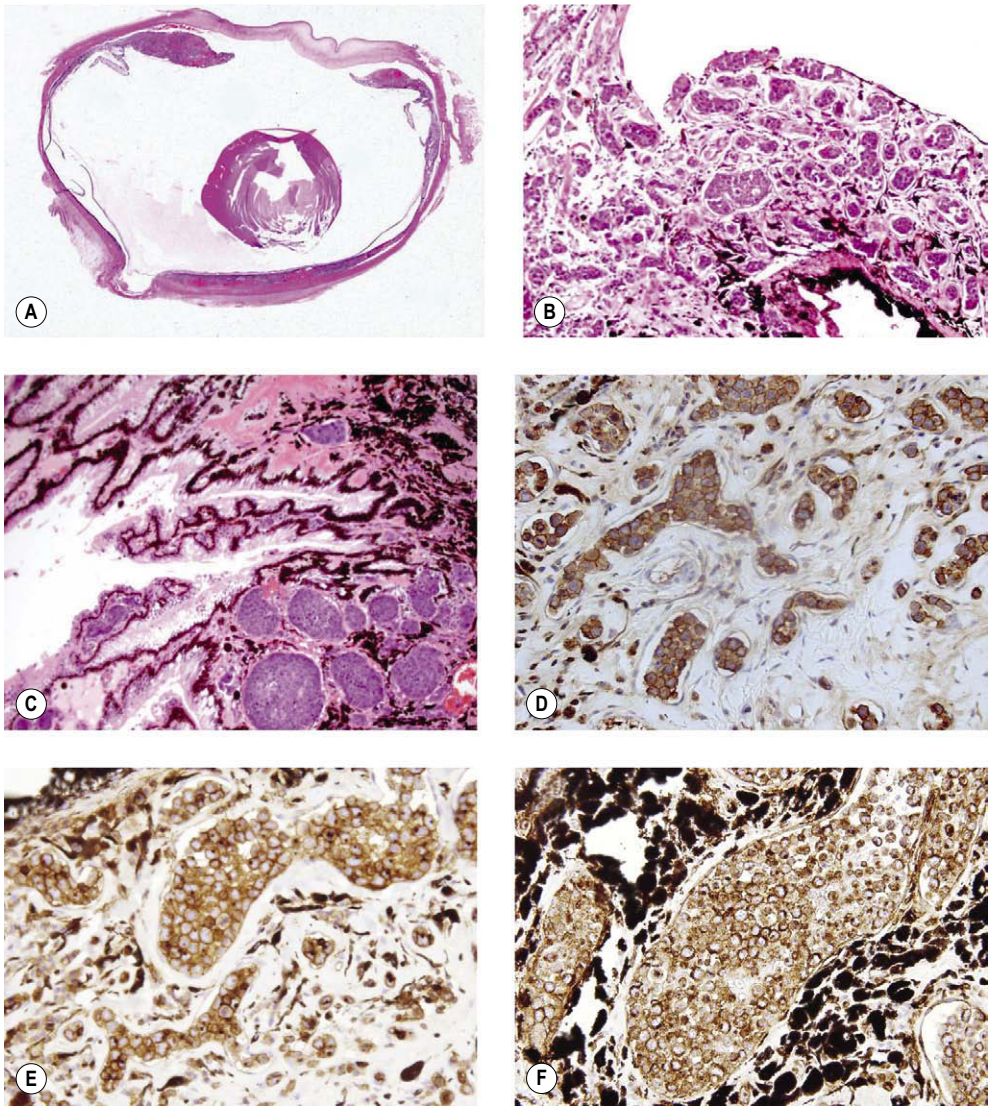


Figure 9.62 Canine intravascular round cell tumor. (A) Subgross photomicrograph showing a canine globe in which the uvea is distorted because of intravascular neoplastic round cells. (B,C) Photomicrographs showing neoplastic cellular infiltrate primarily within the lumina of uveal veins. (D) Immunohistochemistry showing positive staining for CD3 (T cells). (E) Immunohistochemistry showing positive staining for CD18, suggesting a macrophage phenotype. (F) Immunohistochemistry showing positive staining for MHC-II, again suggesting a macrophage phenotype.

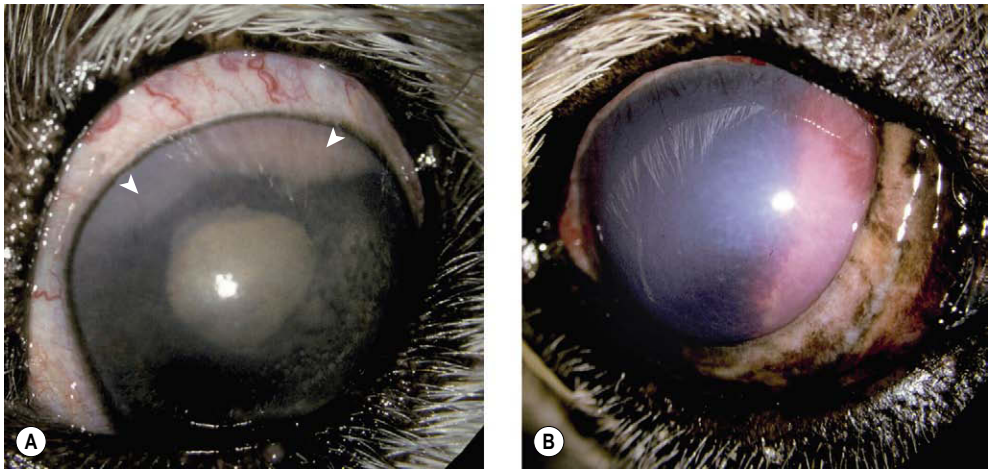


Figure 9.63 Histiocytic sarcoma, clinical. (A) Golden Retriever, 10 years old: the iris is heavily pigmented, but the white iris infiltrate can be seen superiorly (arrows). The masses in the eye and thorax were termed metastatic anaplastic spindle cell tumors. (B) Golden Retriever, 11 years old: the pink mass originated from the iris to fill the nasal anterior chamber.

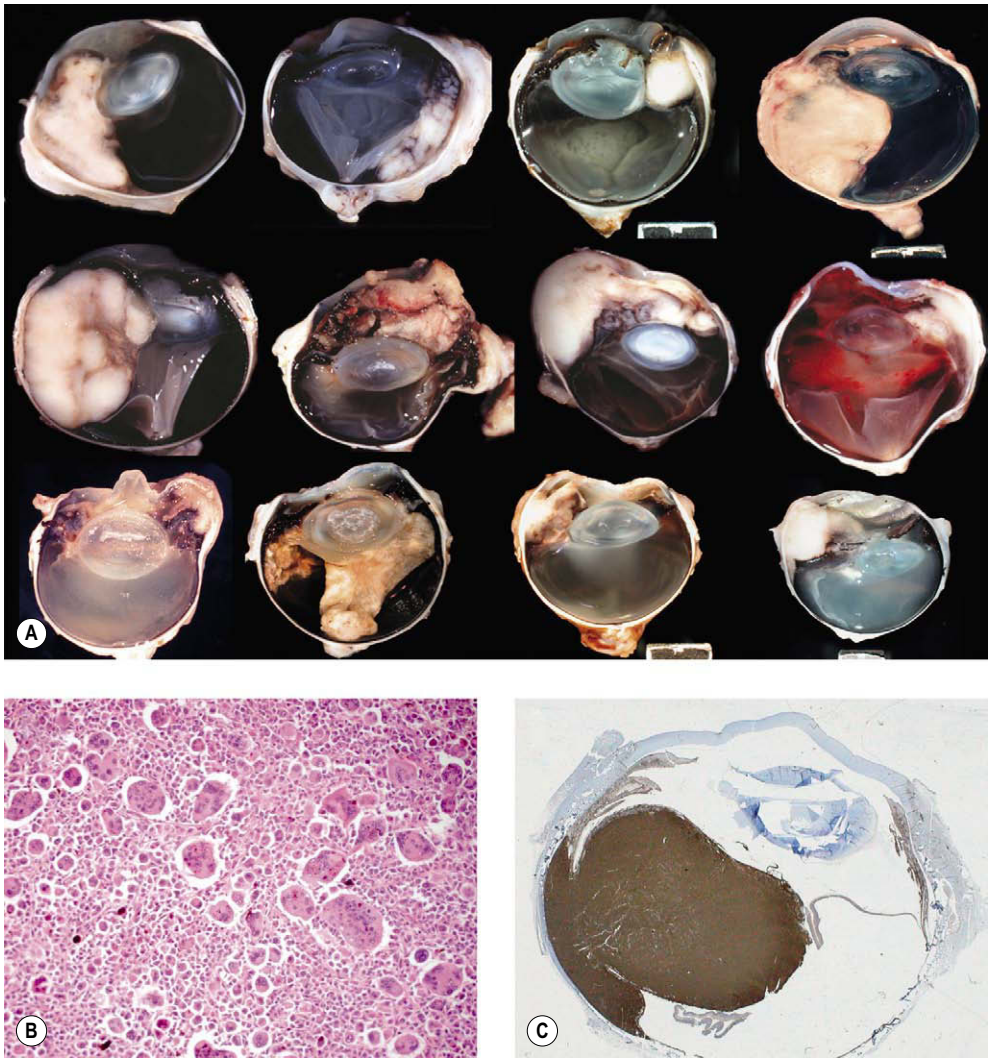


Figure 9.64 Histiocytic sarcoma, pathology. (A) A montage of gross photographs of 12 canine globes with histiocytic sarcoma showing the typical pattern of a large tan mass with extensive segmental infiltration in the globe. (B) High magnification photomicrograph showing the typical appearance of histiocytic sarcoma, including multinucleate giant cells with anaplastic features. (C) Subgross photomicrograph of immunohistochemistry showing positive staining for CD18, a marker for phagocytic cells.

- Tumors identified in pigmented uveal tissue have occurred in animals with partly blue irides or, in one case in which the tumor was located in the choroid, a pigmented iris and non-pigmented choroid

- The signalment of affected dogs may be summarized as follows:
  - The average age of affected dogs is 7.5 years
  - In the 43 cases identified, the following breeds are over-represented:
    - Siberian husky (22 cases)
    - Catahoula hounds (four cases out of a total of 15 Catahoula hounds represented in the COPLOW collection)
- Ocular neoplasia was suspected at the time of submission in less than half of the cases in which SCTBED was diagnosed
- The tumor is usually located in the iris, extending into the ciliary body, but there are also cases entirely confined to the choroid
- The risk of metastasis is still undetermined. However, there are examples of tumors that have recurred in the orbit or within the scleral shell, following enucleation or evisceration, respectively
- Morphologic features of SCTBED include:
  - These tumors lead to a poorly delineated swelling most often within the iris stroma, expanding and distorting the uveal contour
  - The neoplastic cells are spindle cells but they are highly variable in cellular morphology and cellular organization
    - Individual cells range from small, slender spindle cells, devoid of anaplastic features, to large plump cells which exhibit karyomegaly and may be profoundly anaplastic
    - The cellular organization may be consistent with that seen in peripheral nerve sheath tumors (Antoni A and Antoni B patterns)
  - Immunohistochemistry of SCTBED
    - Vimentin positive, suggesting mesenchymal origin
    - S-100 positive, suggesting a neural crest origin
    - GFAP positive in most cases
      - Although considered a marker of astrocytes of the central nervous system, Schwann cells of nonmyelinated nerves are also positively labeled for GFAP. For that reason the GFAP-positive immunolabelling of the majority of SCTBED cases provides strong evidence for a Schwann cell origin of this neoplasm
      - GFAP immunohistochemistry in unaffected, normal canine blue irides demonstrates a plexus of GFAP-positive fibers in the anterior iris and, to a lesser extent in other areas of the uvea, when compared with normal, pigmented iris tissue

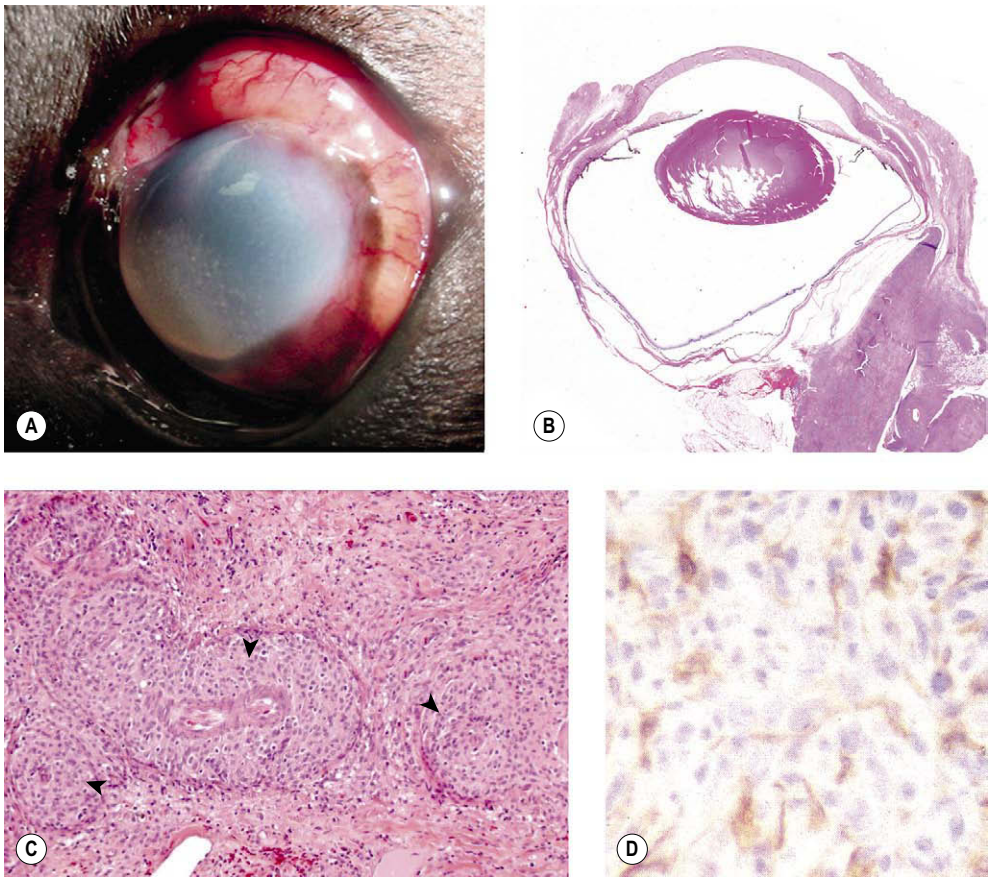


Figure 9.65 Canine systemic histiocytosis. (A) Clinical photograph showing neoplastic mass lesion of systemic histiocytosis distorting the conjunctiva and lid tissues. (B) Subgross photomicrograph showing a canine globe and orbital connective tissues with systemic histiocytosis infiltrating the muscle and loose connective tissues of the orbit. (C) Photomicrograph showing solid sheets of rather bland histiocytic cells effacing the normal tissues. The prominent vasocentric pattern (arrows) is common in systemic histiocytosis. (D) Photomicrograph showing spindle-shaped bland-appearing histiocytes staining positive for CD18, a marker for phagocytic cells.

  - Melan A is usually, but not always negative indicating that the neoplasm is unlikely to be of melanocyte origin, which rules out spindle cell amelanotic melanoma
- There is a solitary, published report of a peripheral nerve sheath tumor with similar morphology in the eye of a dog, but in that report the uvea was pigmented.

Feline post-traumatic ocular sarcoma (FPTOS) (see Ch. 5 for detailed discussion of this neoplasm) (Fig. 9.67)

There are 234 cases in the COPLOW collection, making it the third most common intraocular tumor in cats.

There are three morphologic variants of FPTOS:

1. The spindle cell variant is most common (70% of FPTOS)
   - The spindle cell variant is thought to originate from lens epithelial cells
   - Extension beyond the sclera is a poor prognostic sign
2. The round cell variant (24% of FPTOS) (also discussed later in this chapter)
   - The round cell variant is thought to be a lymphoma
   - Phenotyping the round cell variant FPTOS has proven to be difficult
3. Post-traumatic osteosarcoma or chondrosarcoma (6% of FPTOS)

On average, there is a 7-year latency between a traumatic event with lens capsule rupture and the diagnosis of FPTOS.

Metastasis may occur by the following mechanisms:

- Extension into the orbit leading to local recurrence
- Extension along the optic nerve or peripheral nerves to the brain
- Hematogenous metastasis
- Rarely, metastasis to lymph nodes.

Metastatic neoplasia

- Metastatic pattern in dogs (Figs 9.68, 9.69)
  - Exclusive of lymphoma, there are 223 cases of metastatic neoplasia in canine eyes in the COPLOW collection, accounting for 3.9% of all canine tumors submitted in the COPLOW collection
  - Neoplasms that often metastasize to the eye include histiocytic sarcoma, melanoma, hemangiosarcoma, osteosarcoma, mammary adenocarcinoma, as well as many others
  - Common morphologic features of metastatic neoplasia in the canine eye include:
    - Metastases may be present in one globe but recurrent tumor in the second globe is common
    - A tendency to affect the anterior uvea more than the choroid
    - Neoplastic cells are often identifiable in blood vessels
    - Neoplastic cells 'break out' from the uveal stroma and 'line' the anterior or posterior chambers

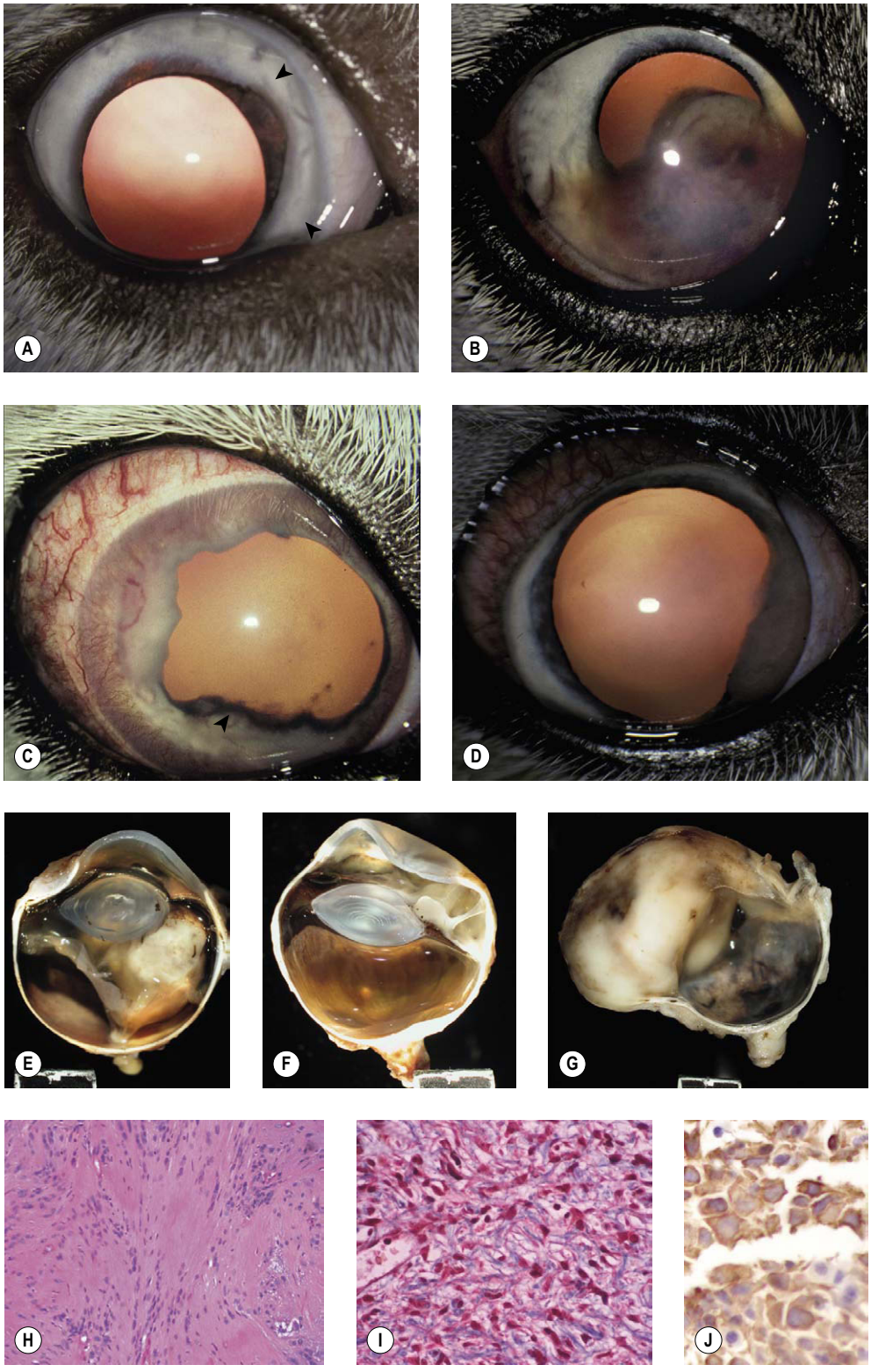


Figure 9.66 Spindle cell tumor of blue-eyed dogs (SCTBED). (A) Siberian Husky, 4 years old: a subtle loss of iris architecture nasally (arrows) was the only abnormality in this early case. The prominent iris pigment may have been congenital. (B) Siberian Husky, 4.5 years old: the inferior anterior chamber is filled with the iris mass, associated fibrin, and hemorrhage. (C) Siberian Husky, 7 years old: the limbal cornea is vascularized. The entire iris is infiltrated resulting in dyscoria and posterior synechia (arrow). (D) Australian Shepherd, 12 years old: this nasal mass was originally diagnosed as a neurofibrosarcoma of the iris. (E,F) Gross photographs of globes from two dogs with spindle cell tumor of blue-eyed dogs. (G) Gross photograph showing the scleral shell from a dog that had an evisceration in a globe with SCTBED. The tumor re-grew, leading to removal. (H) Photomicrograph of SCTBED showing a cellular arrangement typical of the Antoni B pattern of schwannoma (H&E). (I) Photomicrograph of a trichrome-stained SCTBED showing a delicate interplay between collagen (blue) and cellular cytoplasm (red). (J) Immunohistochemistry showing GFAP-positive staining, suggesting that the SCTBED is a tumor of the Schwann cells of non-myelinated nerve fibers.

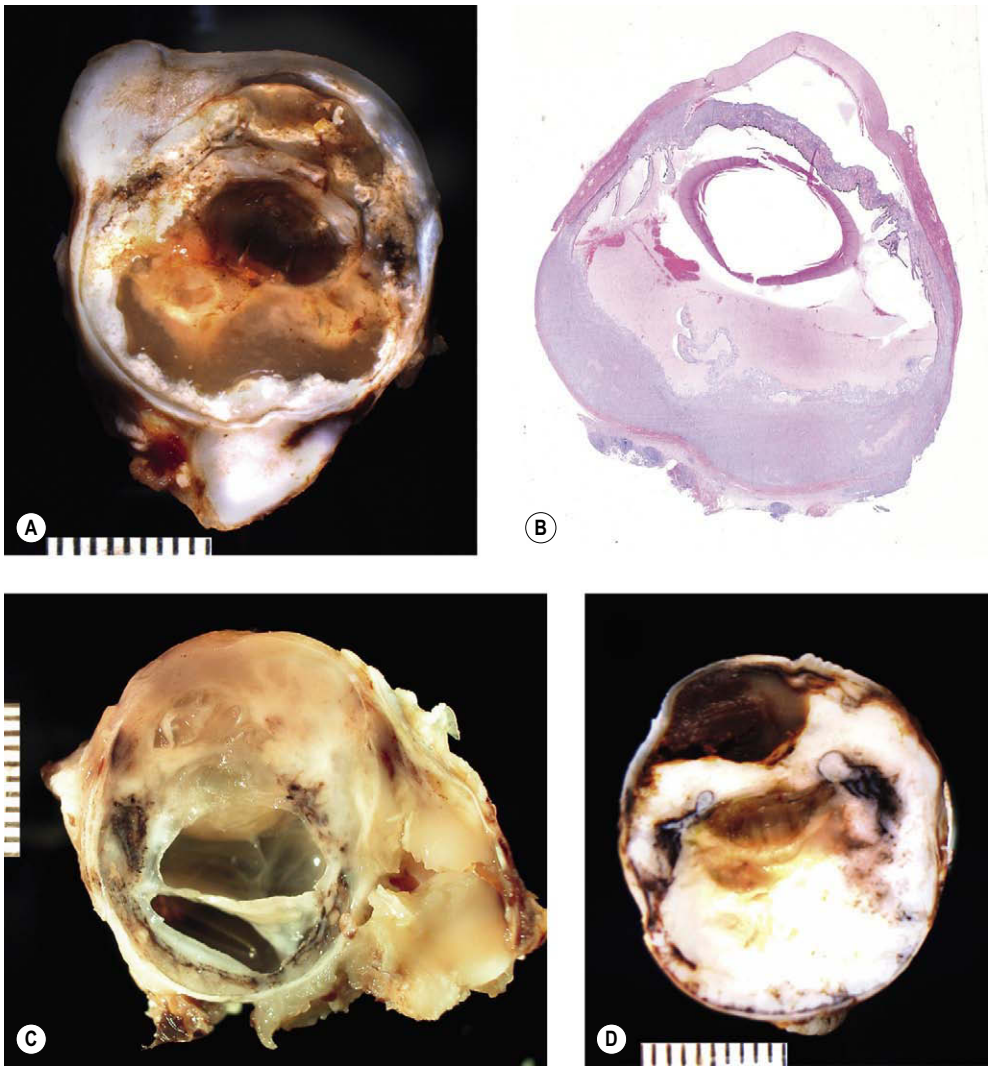


Figure 9.67 Feline post-traumatic ocular sarcoma (FPTOS), pathology (A) Gross photograph showing spindle cell variant FPTOS. The tumor is distributed diffusely around the inside of the globe and extends through the sclera and into the optic nerve. (B) Subgross photograph showing spindle cell variant of FPTOS. (C) Gross photograph showing round cell variant of FPTOS. The pattern of diffuse infiltration within the globe and extension beyond the sclera is common to all three variants of FPTOS. (D) Gross photograph showing osteosarcoma variant of FPTOS. The globe has the same tumor distribution.

  - In some cases, thorough evaluation fails to reveal a primary neoplasm and diagnosis of a rare primary ocular malignant neoplasm, such as extraskeletal osteosarcoma or chondrosarcoma, may be made.
- Metastatic pattern in cats (Figs 9.70, 9.71)
  - Exclusive of lymphoma, there are 101 cases of metastatic neoplasia in feline eyes in the COPLOW collection, accounting for 3.7% of all feline COPLOW submissions with neoplasia
  - Common morphologic features of metastatic neoplasia in cat eyes include:
    - Uveal metastases may be recognized in one or both globes
    - A tendency to affect the choroid more often than the anterior uvea
    - When the anterior uvea is affected by metastatic epithelial tumors, the neoplastic cells form a 'lining' attached to the inner surface of the iris and ciliary body
    - There is often extensive and widespread invasion of blood vessels
    - A pattern of choroidal infarction is often seen, with characteristic, wedge-shaped areas of tapetal discoloration and profound vascular attenuation visible on funduscopy
    - Orbital involvement may accompany involvement of the posterior segment of the globe
    - Ocular metastases may be diagnosed in cats with many forms of malignant neoplasia; with pulmonary carcinoma, squamous cell carcinoma of undetermined origin, and fibrosarcoma being seen most commonly.

Comparative Comments

Metastatic carcinoma of the choroid is the most common intraocular malignant tumor in humans. The most common primary site of choroidal metastases in males is the lung and in females the breast. These tumors may mimic amelanotic or lightly pigmented choroidal melanomas and are distinguished on the basis of history, systemic workup, fluorescein angiography, ultrasonography, and fine needle aspiration biopsy when necessary.

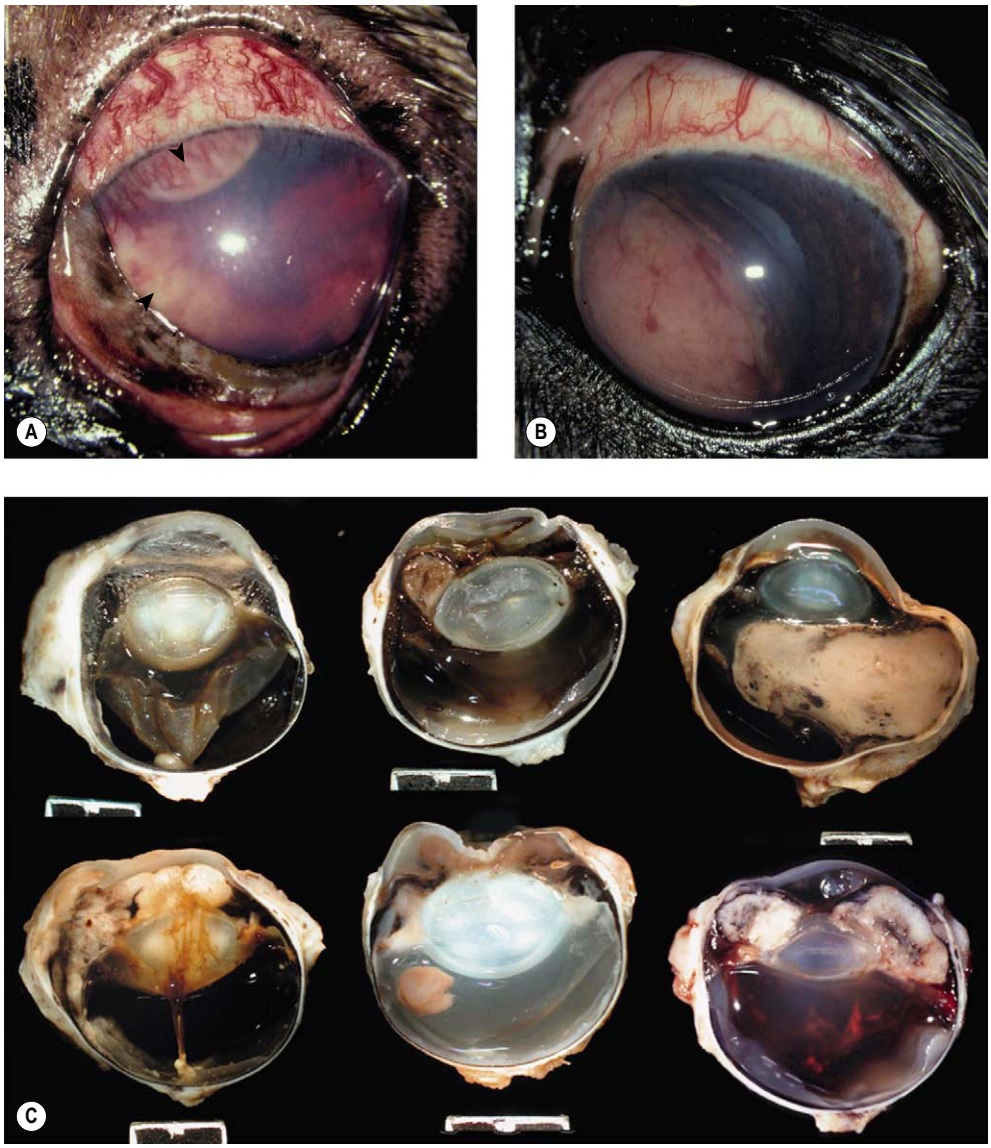


Figure 9.68 Metastatic tumors to the eye, canine. (A) Golden Retriever, 11 years old: this was diagnosed as a metastatic hemangiosarcoma. In addition to the severe hemophthalmos, two areas of white infiltrate are present (arrows). (B) Skye Terrier, 10 years old: the blood-tinged white mass was diagnosed as a metastatic amelanotic melanoma. (C) A montage of gross photographs of six canine eyes showing metastatic tumors. These tumors are characteristically in the anterior uvea and anterior segment.

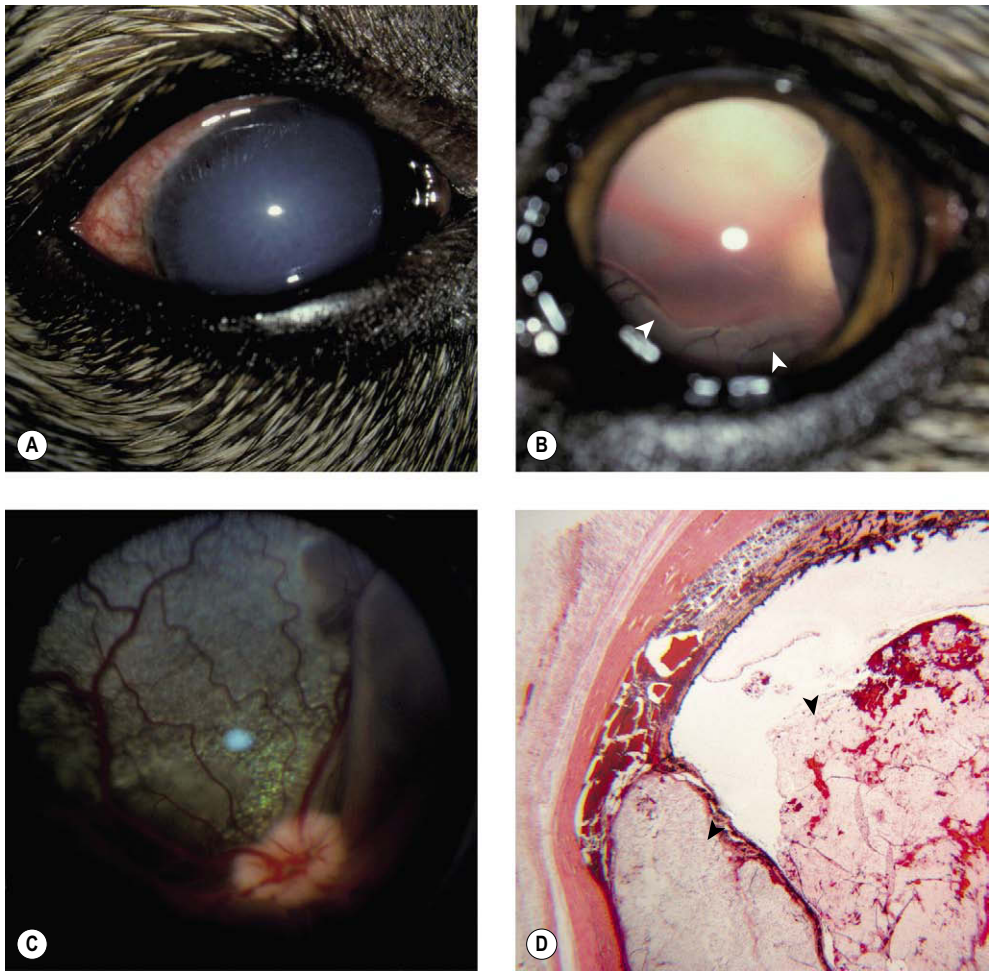


Figure 9.69 Metastatic osteosarcoma case. (A) Australian Shepherd cross, 5 years old: severe corneal edema prevented visualization of anterior segment. Some 4 months prior to this photograph, a leg was amputated. Both globe and bone neoplasias were diagnosed as osteosarcoma. (B) Left eye of the dog in (A), 3 months later. The dark area at the pupil margin and the cloudy area inferior (arrows) represent retinal elevations. (C) Fundus photograph of the eye in Figure 9.69B. A misshapen optic nerve and superior temporal retinal elevation. Osteosarcoma was again diagnosed on histopathology. (D) Low magnification photomicrograph of the same dog as (A) shows osteosarcoma invading the uvea (arrows).

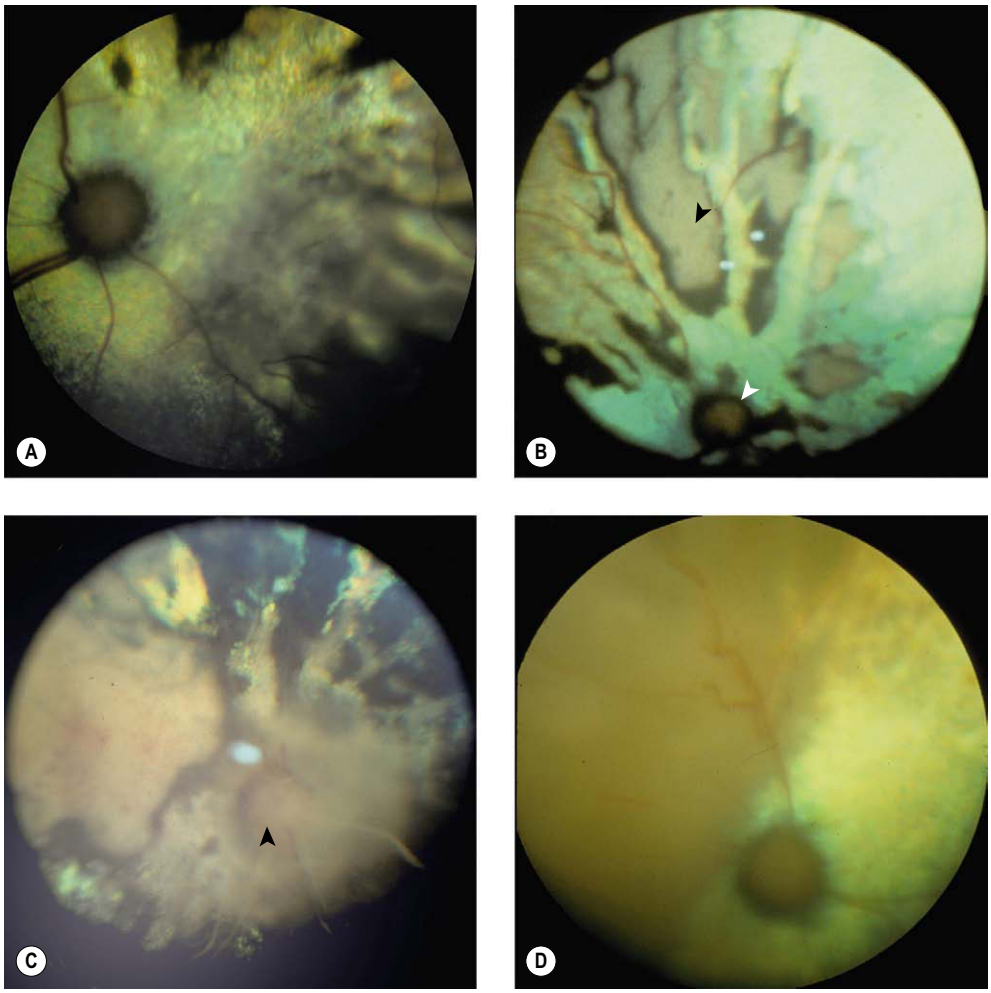


Figure 9.70 Metastatic tumors to the eye, feline, fundus. (A) DSH, 13 years old: metastatic angioinvasive squamous cell carcinoma was diagnosed as the cause of the abnormal tapetal coloration and retinal edema. (B) DSH, 14 years old: a metastatic intestinal adenocarcinoma was diagnosed in the retina and choroid accounting for the sheets of gray discoloration (black arrow). The optic disc (white arrow) was also infiltrated. (C) DSH, 15 years old: a metastatic carcinoma was the etiology for the severe cellular infiltrate surrounding the optic disc (arrow). Tumors cells were found in the choroid, retina, and optic nerve meninges. (D) DSH, 17 years old: a metastatic adenocarcinoma of the sweat glands was the diagnosis of the choroidal and subretinal involvement, leading to the retinal detachment.

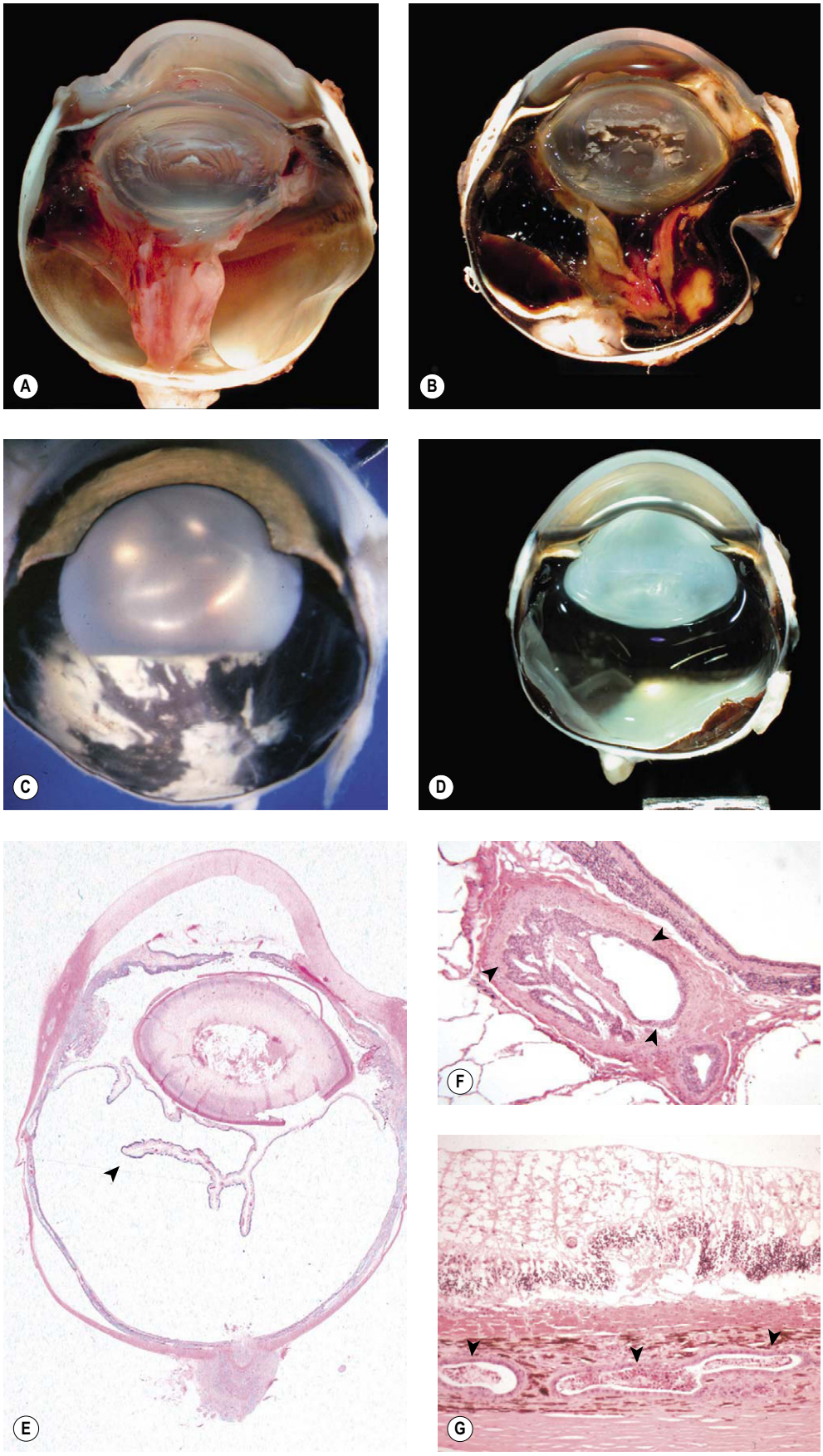


Figure 9.71 Metastatic tumors to the eye, feline, pathology. (A,B) Gross photographs showing how metastatic tumors in feline globes characteristically involve the choroid with retinal detachment. (C) Gross photograph showing the posterior segment from a feline globe with chorioretinal metastatic pattern. (D) Gross photograph of a feline globe showing choroidal thickening associated with metastatic neoplasia. (E) Subgross photomicrograph of a metastatic epithelial tumor showing a line of basophilic metastatic tumor (arrow) surrounding the detached retina and the anterior uvea. (F) Photomicrograph from a primary lung tumor showing the angioinvasive nature of the tumor. A pulmonary artery is lined by neoplastic epithelium (arrows). (G) Photomicrograph showing the retina and choroid from a feline globe with choroidal angioinvasive metastatic carcinoma (arrows).

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Chapter 10

Diseases of the Lens

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NORMAL ANATOMY (Fig. 10.1)

- The lens has only one cell type, the lens epithelial cell
- At all stages of lens development, except embryonic, normal lens epithelial cells are only present anteriorly, where they form a monolayer of cuboidal epithelium (Chapter 3 provides a more detailed discussion of lens development)
- At the lens equator, the lens epithelial cell elongates, rotates and is pushed inward. The cell then continues to elongate until the anterior and posterior tips of each lens fiber reach opposite poles of the lens. The fully differentiated lens fiber cells lose their nuclei and become compacted towards the center of the lens, as new fibers continue to form throughout life
- The lens is surrounded by a thick capsule which represents the basement membrane of the lens epithelium. Throughout life, the anterior lens capsule continues to thicken while the posterior capsule remains thin, since there are no lens epithelial cells at the posterior pole
- In mammals, the lens is held in place on the anterior vitreous face by a combination of the gentle pressure exerted from behind by the vitreous body, and the tension of zonular ligaments that suspend the lens circumferentially. These zonules are secreted by the ciliary epithelium and insert in a crossover pattern onto the equatorial lens capsule.

Comparative Comments

- The lens is a simple structure histologically and in the human generally conforms to the description given for the lens in other species
- The remarkable complexity of the lens is hidden at the molecular and functional levels.

CONGENITAL OR HEREDITARY CONDITIONS (see Ch. 3)

Posterior lenticonus/lentiglobus (Fig. 10.2)

- Posterior lenticonus or lentiglobus is characterized by the localized axial elongation and increased curvature of the

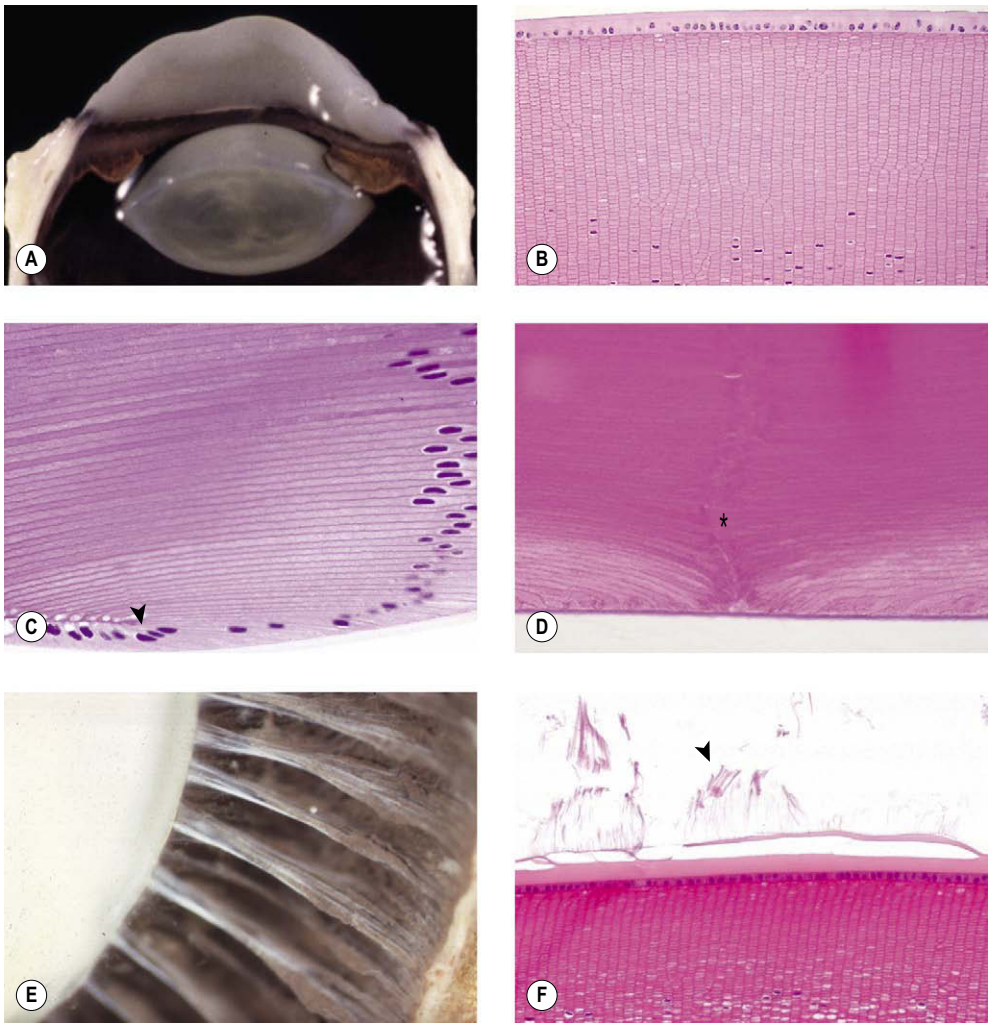


Figure 10.1 The normal lens. (A) Gross photograph of normal canine lens in place *in situ*. (B) Photomicrograph of the anterior pole of a Davidson's-fixed canine lens showing crisp outlines of individual lens fibers. (C) Photomicrograph of canine lens showing the equatorial lens nuclear bow. Cuboidal lens epithelial cells from the anterior pole first elongate, rotate and then become incorporated into the lens cortex (arrow). (D) Photomicrograph showing the posterior pole and posterior suture (*) of a canine lens in a Davidson's-fixed specimen. (E) Gross photograph of a canine globe sectioned across the equator and postfixed in acetic acid to make the zonular ligaments more opaque. The photograph shows the distribution of zonular fibers. (F) Photomicrograph of the lens equator showing remnants of zonular ligament fibers (arrow).

posterior lens, leading to a conical or spherical protrusion of the posterior pole of the lens
- Stretching, thinning or discontinuity of the posterior capsule are frequent findings in posterior lenticonus/lentiglobus.

Aphakia, microphakia, lens coloboma (Fig. 10.3)

- Congenital absence of the lens, an abnormally small lens, or an irregular lens shape may result from developmental abnormalities affecting the orientation, induction and separation of the lens vesicle. Microphakia and irregularities of lens shape can be seen alone or, more often, as a part of a syndrome of developmental abnormalities involving the anterior segment of the globe
- Diffuse or focal lack of zonular tension at the lens equator may result in spherophakia or so-called lens coloboma respectively. These abnormalities in lens shape probably do not represent primary abnormalities in lens development, rather they are associated with anterior segment developmental abnormalities that affect the ciliary processes and zonular integrity.

Congenital cataract (Figs 10.4, 10.5)

- Morphologic features which typify congenital cataract include:
  - Cataractous changes in the lens nucleus characterized by an abnormal position of the nucleus or lysis of the nucleus
  - Abnormal relationship between the epithelium and lens capsule such as duplication, wrinkling, or segmental changes
  - Posterior migration of lens epithelial cells
  - Vascular or pigmented structures adherent to the lens capsule might indicate a cataract associated with abnormal development of the fetal vasculature (persistent pupillary membranes, persistent hyperplastic primary vitreous, or persistent hyperplastic tunica vasculosa lentis)
- Congenital cataract and associated ocular abnormalities, that may include microphthalmia syndromes and abnormalities in the fetal hyaloid vasculature, are described in detail in Chapter 3.

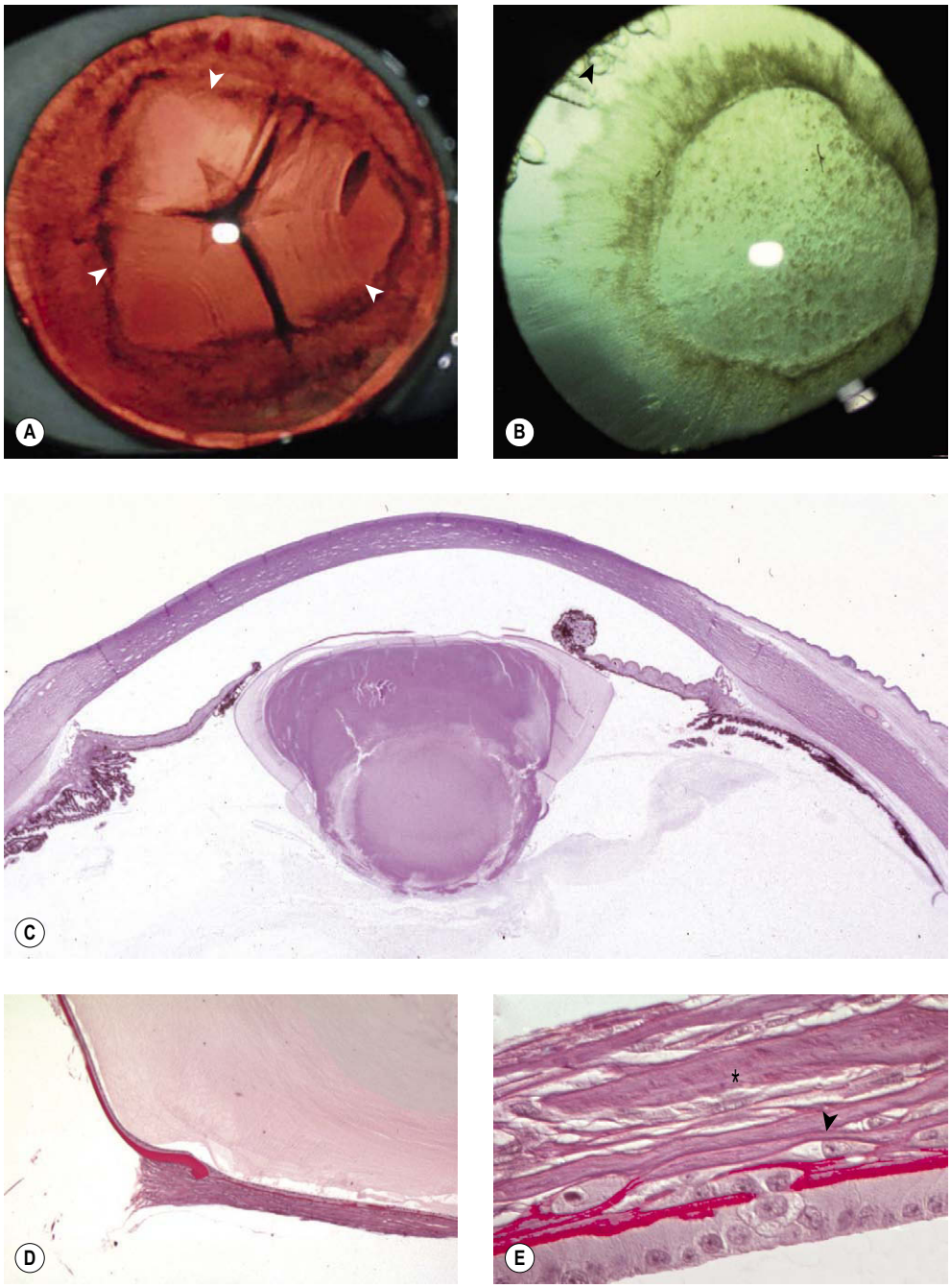


Figure 10.2 Lenticonus. (A) Siberian Husky, 18 months old: the arrows delineate the area of posterior lenticonus. (B) Newfoundland, 1 year old: the dark irregular circle represents the area of lenticonus. Radiating cortical opacities and water vacuoles (arrow) are also present at the lens equator. (C) Low magnification photomicrograph of an equine eye showing posterior lenticonus. (D,E) Photomicrographs of the posterior pole from the same eye as (C) showing a complex relationship between the lens capsule and the proliferating lens epithelium. In (E), the lens epithelium has undergone spindle cell metaplasia (arrow) and collagen deposition (*).

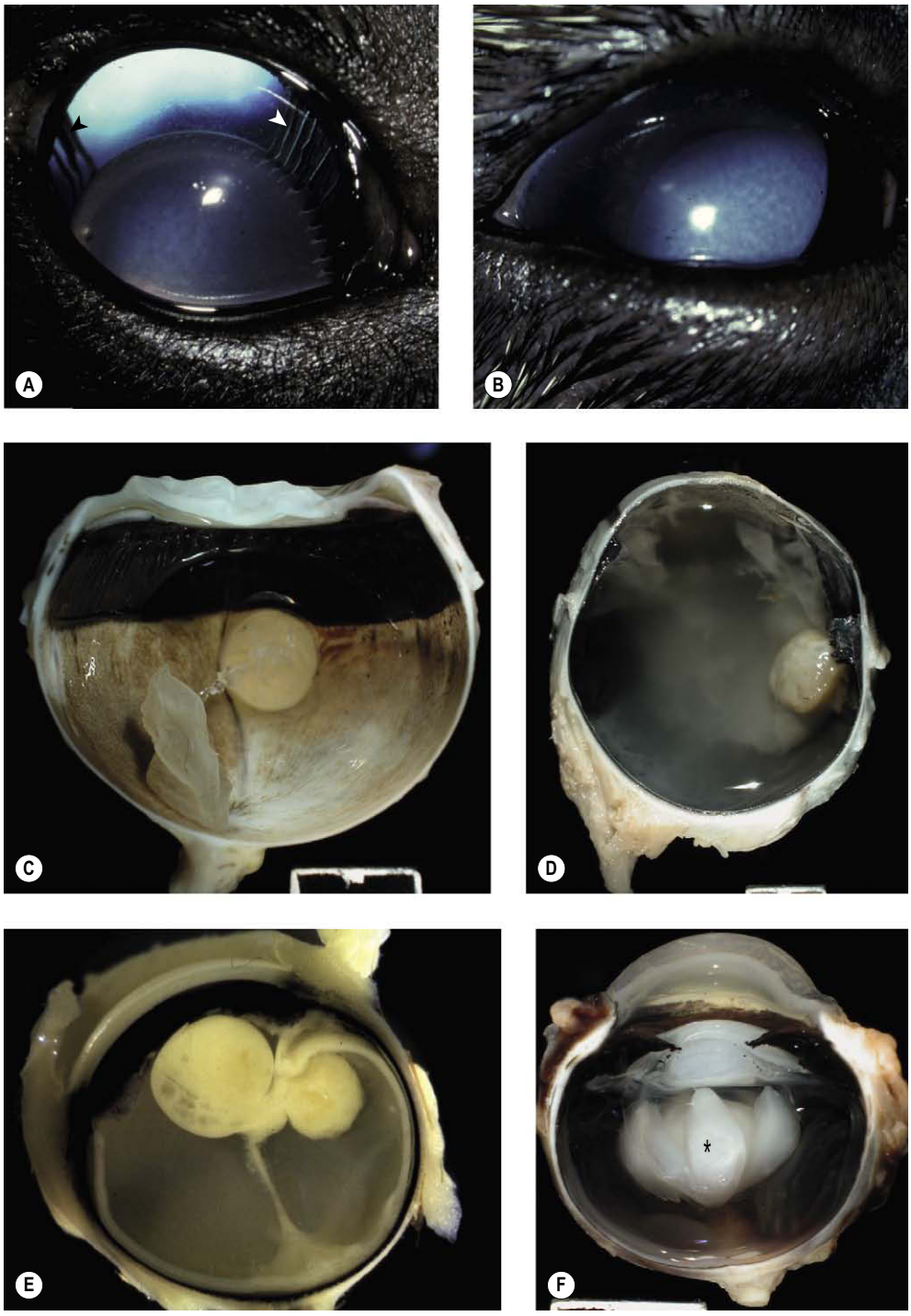


Figure 10.3 Developmental problems of the lens. (A) Dachshund, 4 months old: in addition to being small, the lens was also rounder than normal (spherophakic). The ciliary processes with zonular fibers can be seen at both arrows. (B) German Shepherd Dog, 6 months old: the small round lens luxated totally into the anterior chamber, resulting in corneal edema. (C) Gross photograph of a canine globe with microphakia. (D) Photomicrograph of an equine globe with microphakia. (E) Bouin's-fixed ferret globe with lens coloboma. (F) Gross photograph of canine globe with microphakia and posterior capsular rupture. Opaque lens proteins exude into the vitreous (*).

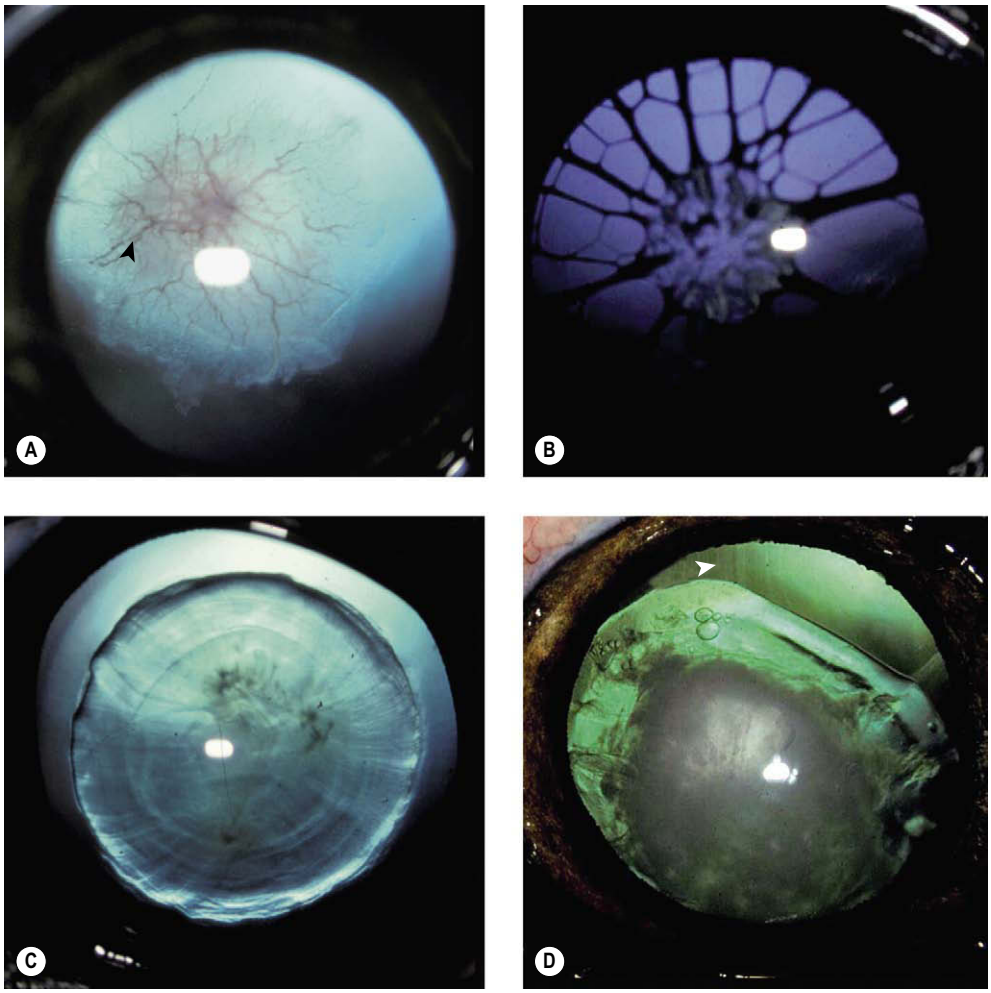


Figure 10.4 Congenital and early onset cataract, clinical. (A) Labrador Retriever, 10 weeks old: posterior capsular and cortical opacity resulted from the persistent hyaloid artery and its branching vessels, persistent hyperplastic tunica vascularis lentis (arrow). (B) Great Dane, 8 weeks old: multiple persistent pupillary membranes attached to the axial anterior lens creating an anterior capsular opacity. (C) Boston Terrier, 3.5 months old: the diffuse nuclear opacity with clear cortex was present in both eyes. (D) Bassett Hound, 3 years old: the lens nucleus is totally opaque with diffuse cortical opacities. The lens has an irregular shape (coloboma). Fine zonular fibers are present only segmentally (arrow).

Comparative Comments

- In man, as in animals, in addition to the congenital and hereditary abnormalities, primary aphakia with complete failure of lens formation has been reported in rare instances. More commonly, a small or incompletely formed lens, giving the clinical impression of aphakia, has been observed
- Other congenital abnormalities that are also seen the human lens include conditions of imperfect or delayed lens-corneal separation, anterior lenticonus, and spherophakia. In the latter condition, the lens is relatively more rounded than normal and usually smaller (microphakic)
- An important congenital condition in humans is rubella cataract, which occurs in the fetus if the mother is exposed to rubella virus during the first or second trimester of pregnancy. Rubella virus may be cultured from surgically removed lenses
- Although tumors of the lens do not occur in humans, the lens anlage has been reported to develop aberrantly in the lower lid, in a condition known as phakomatous choristoma.

CATARACT

- Cataract is the pathological opacification of the lens including its capsule
- Cataract may be categorized according to extent of lens involvement, location within the lens, or etiopathogenesis.

Cataract categorized by the extent of disease (Figs 10.6–10.10)

- Incipient cataracts involve less than 15% of the lens
- Immature cataracts affect more than 15% of the lens but lens involvement is incomplete and they do not completely obscure the fundus reflection
- Mature cataracts affect the lens cortex *circumferentially* and completely obstruct visualization of the fundus reflection
- Hypermature cataracts show evidence of lens shrinkage, such as lens capsule wrinkling, associated with leakage and resorption of altered cortical lens proteins.

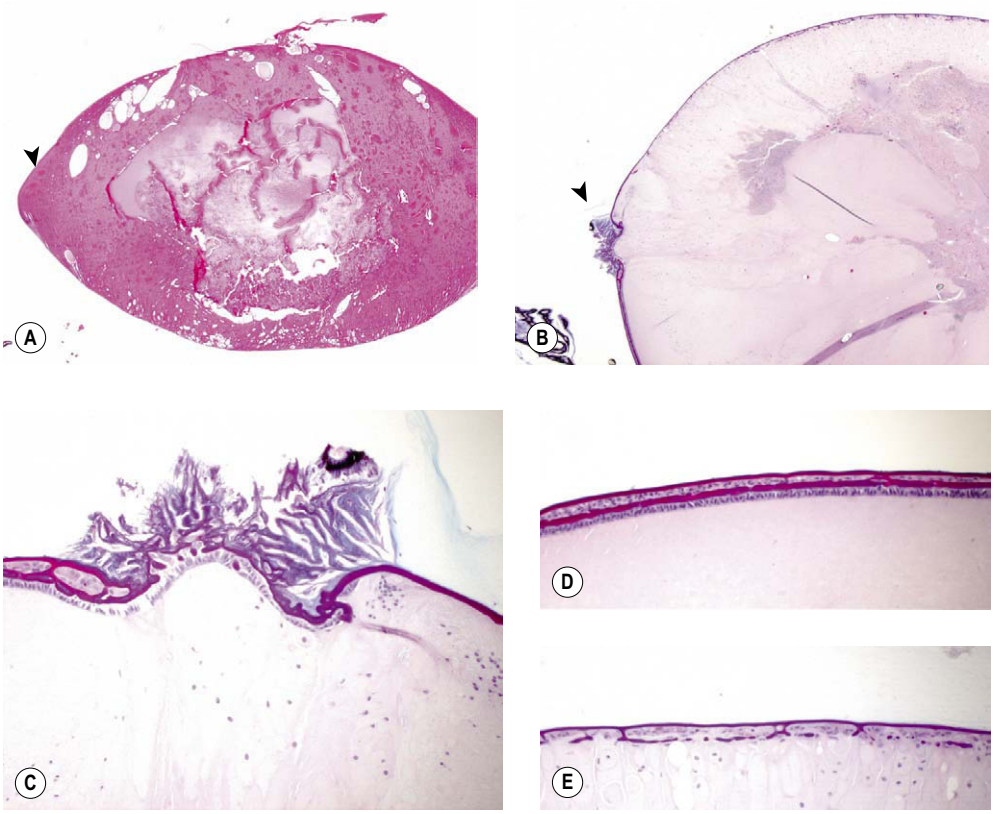


Figure 10.5 Congenital cataract, pathology. (A) Low magnification photomicrograph of a dog lens with congenital cataract. The cataractous changes are predominantly nuclear. The posterior pole and the equatorial cortex remain near normal (arrow). (B) Low magnification photomicrograph showing a focal dysplastic and wrinkled lens capsule (arrow). (C) The same focus as (B) with higher magnification showing the relationship between the duplicated lens capsule and the lens epithelium. (D,E) Two photomicrographs of the anterior poles of two lenses showing duplications in the lens capsule and lens epithelium in canine congenital cataracts.

Cortical cataract, the opacification of the lens fiber (Fig. 10.11)

- There is not a perfect correlation between the clinical observation of lens opacity and a histologically observable morphologic change in the lens cortex
  - Many changes in the lens protein can represent either genuine pathology or artifact of processing. Therefore, it may be impossible to determine the significance of observed morphologic changes
  - Reliable morphologic indicators of cortical cataract include:
    - Bladder cells: swollen, rounded lens fibers that still contain a nucleus
    - Morgagnian globules: swollen, rounded lens fibers with no nucleus
  - Lens mineralization may occur in long-standing cataracts.

Subcapsular cataract, opacification and metaplasia of the lens epithelial cell (Fig. 10.12)

- Normal lens epithelial cells are positioned immediately adjacent to the lens capsule and their tropism for the lens capsule is seldom altered in disease states
- In subcapsular cataract the opacity is directly related to abnormalities of the lens epithelial cells
- Morphologic features of subcapsular cataract include:
  - Proliferation of lens epithelial cells to form a localized aggregate
  - Metaplasia, involving a change in the cells from an epithelial phenotype to a mesenchymal phenotype more characteristic of a myofibroblast
  - Secretion of collagen around the metaplastic lens epithelial cells
  - Loss of the lens epithelial cells leaving behind cell-free collagen matrix
  - Mineralization.

Inherited cataract in dogs

- Inherited cataract is very common in the purebred canine population. An inherited basis for cataract development is proven or suspected in over 100 canine breeds, of which many appear to demonstrate complex patterns of inheritance. In some canine breeds, a genetic basis for cataract development has been clearly established, e.g. mutations in the *HSF4* gene are associated with early-onset cataract in several breeds, including the Staffordshire bull terrier and Boston Terrier
- Clinical phenotype is highly variable between and within affected breeds. This variability may result from the influence of multiple genes and other metabolic and environmental factors.

Age-related cataract

- Cataracts are a common feature of senescence in most species
- Senile cataracts should be distinguished, both clinically and histomorphologically, from the normal process of nuclear sclerosis which is not associated with true lens opacity
- In nuclear sclerosis, the density of the lens nucleus increases with age as older lens fibers are progressively tightly packed centrally and take on a more homogeneous in appearance, as new cortical fibers are formed more peripherally.

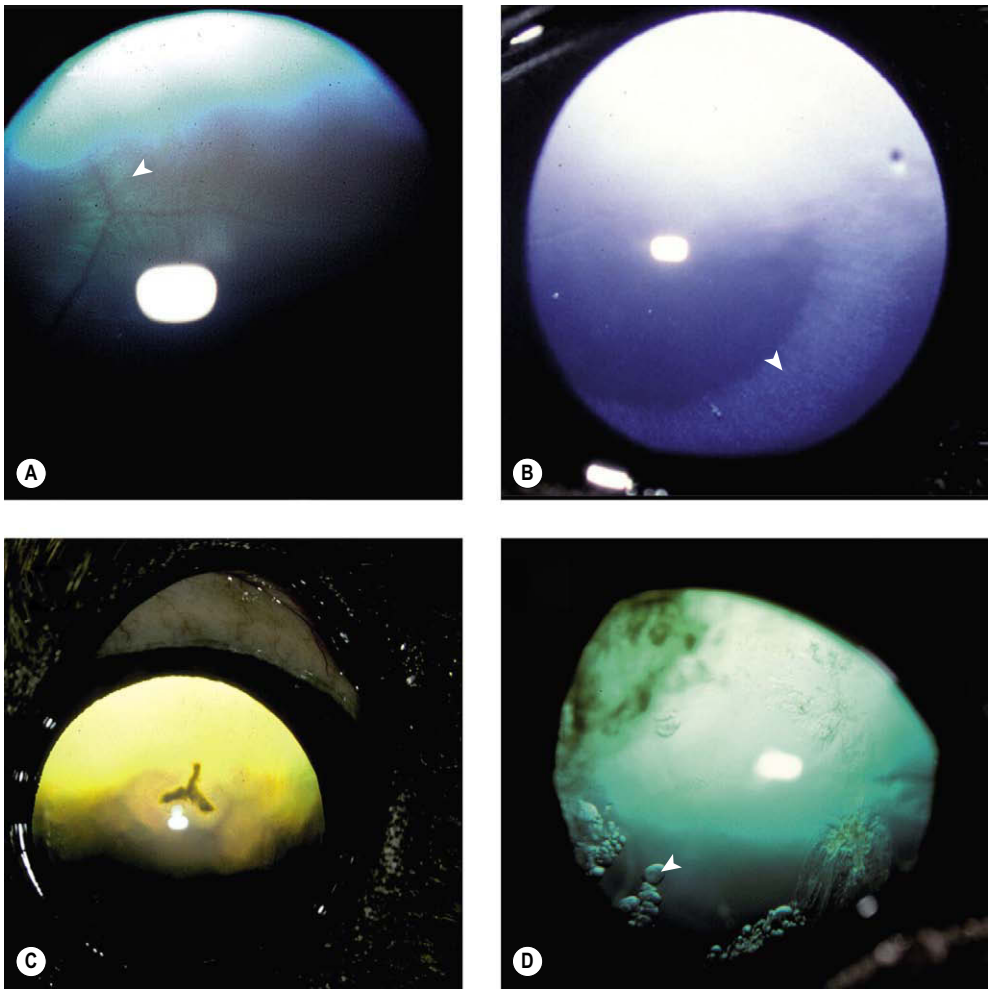


Figure 10.6 Incipient cataracts, clinical. (A) Siberian Husky, 10 months old: feathering along the posterior cortical suture lines (arrow) was present in both lenses. (B) Cavalier King Charles Spaniel, 8 weeks old: the equatorial cortex was overhydrated (arrow) in this immature cataract. This overhydration cleared in the adult. (C) Golden Retriever, 3 years old: the posterior cortical suture is opaque as was the axial subcapsular cortex surrounding the suture line. (D) Italian Greyhound, 5 years old: equatorial cortical water vacuoles are present (arrow). The opacity at 10 o'clock represents vitreous degeneration.

Secondary cataract

- Cataract may occur secondary to other intraocular disease; such as uveitis, glaucoma, neoplasia or advanced retinal degeneration; or as a result of trauma, electrocution, nutritional imbalance, exposure to toxins or metabolic disease, such as diabetes mellitus.
- Metabolic cataract is recognized in almost all diabetic dogs (Fig. 10.10)
  - Diabetic dogs are far more likely to develop cortical cataract because of the conversion of glucose to sorbitol within the lens cells and the resulting influx of water
  - Diabetic cataracts often develop rapidly and can lead to serious inflammatory changes if the lens capsule ruptures (see below) or to secondary glaucoma caused by lens swelling (intumescent cataract)
  - The diabetic state can also contribute to complications following cataract surgery
    - In general, however, substantial differences in post-operative outcomes are not apparent compared to non-diabetic dogs
  - Although diabetic cataracts are usually cortical cataracts, there are no specific morphologic features which allow a diabetic cataract to be distinguished from any other cortical cataract morphologically
  - Although diabetes mellitus is fairly common in cats and humans, diabetic cataract is not common in these species
    - The lower incidence of diabetic cataract in cats may relate to lower levels of activity of the enzyme aldose reductase in the lens of older cats, compared to dogs.

Comparative Comments

- The types of cataracts occurring in humans and other species appear to be extremely similar, although they have been further subdivided into a greater number of types in humans
- An extremely interesting entity is the exfoliation syndrome, also known as pseudoexfoliation, in which a fibrillary protein-like material is deposited on the anterior lens capsule
- The major systemic disorders associated with cataract development in humans are diabetes mellitus, galactosemia, hypercupremia, Fabry disease and Down syndrome
- Numerous drugs give rise to cataracts in humans, the most common being corticosteroids.

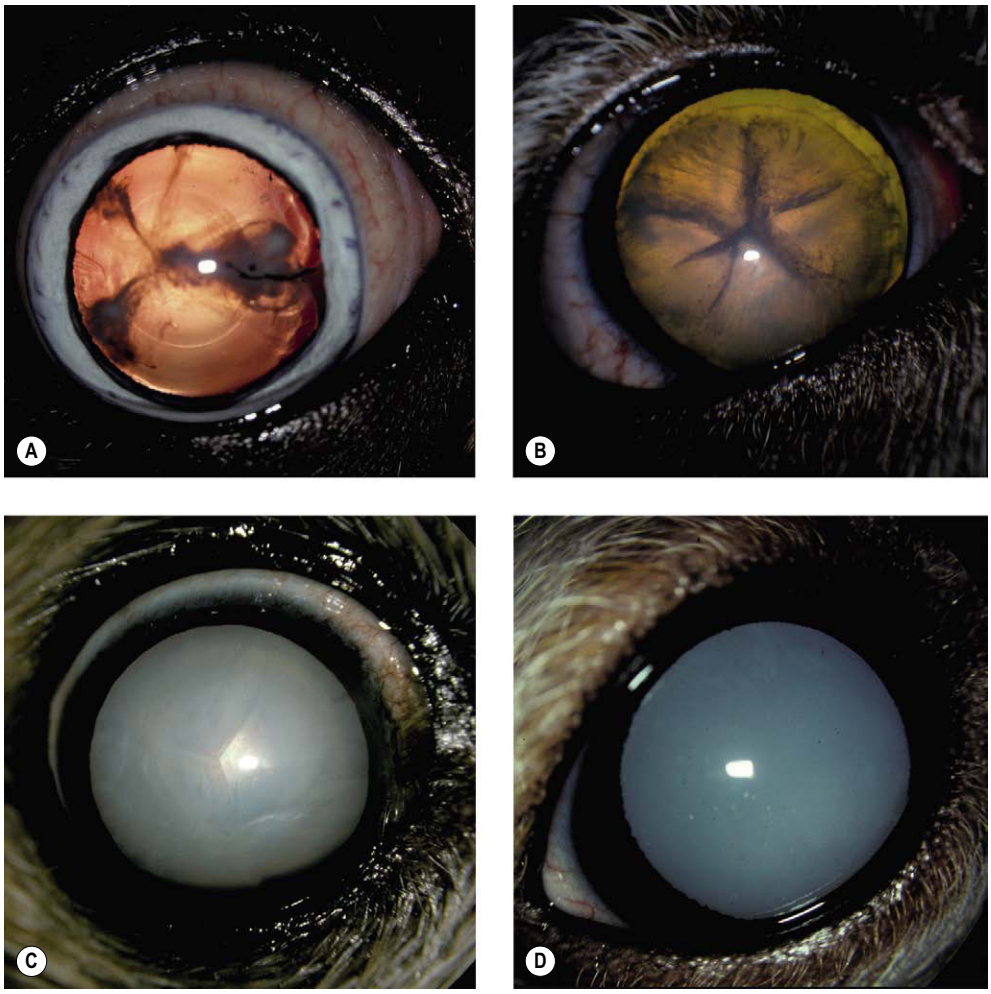


Figure 10.7 Immature and mature cataracts, clinical. (A) Boston Terrier, 7 years old: anterior and posterior cortical opacities are present and radiate to the lens equator. (B) Cockapoo, 5 years old: the cortical suture lines are opaque. Diffuse cortical and nuclear opacities appear dark due to retroillumination from the tapetal reflection. (C) Pomeranian, 15 years old: the entire lens is opaque with no visible tapetal reflection in this mature cataract. (D) Poodle, 6 years old: the homogenous appearance of the cataract is due to lens liquefaction in this hypermature cataract.

LENS PROTEIN BREAKDOWN OR LENS CAPSULE RUPTURE AND ITS SIGNIFICANCE IN INFLAMMATORY EYE DISEASE

Morphologic features suggesting pathologic lens capsule rupture (Fig. 10.13)

- Recoil or scrolling of the ends of the lens capsule is a feature that distinguishes pathologic rupture from artifact
- Entrapment or digestion of lens capsule at the site of rupture is a feature of pathologic rupture
- If the lens capsule remains intact, then there should be no cell type other than lens epithelial cells or metaplastic lens epithelial cells within the capsule
  - Characteristic cells to look for, that suggest pathologic lens capsule rupture, include the following:
    - Macrophage cells
    - Neutrophils
    - Red blood cells
    - Fibroblasts and blood vessels.

Phacolytic uveitis (lens-induced uveitis) (Fig. 10.14)

- Phacolytic uveitis occurs in response to the 'broken down' lens proteins that characterize cataract, particularly mature and hypermature cataract. These altered lens proteins are able to leak through an intact lens capsule into the aqueous inciting a mild to moderate inflammation
- There is a mild to moderate lymphoplasmacytic uveitis
- Subsequent formation of extensive posterior synechiae with iris bombé, or peripheral anterior synechiae, increases the risk of secondary glaucoma
- Apparent leakage of lens-related granular protein occurs in a small percentage of cats with idiopathic lymphoplasmacytic uveitis.

Phacoclastic uveitis

- In phacoclastic uveitis, inflammation occurs in response to the sudden release of relatively large quantities of lens protein after lens capsule rupture
- In our opinion, the true incidence of phacoclastic uveitis, not associated with pathologic organisms such as bacteria, is hard to determine because bacteria are often identified within ruptured lenses (see below)

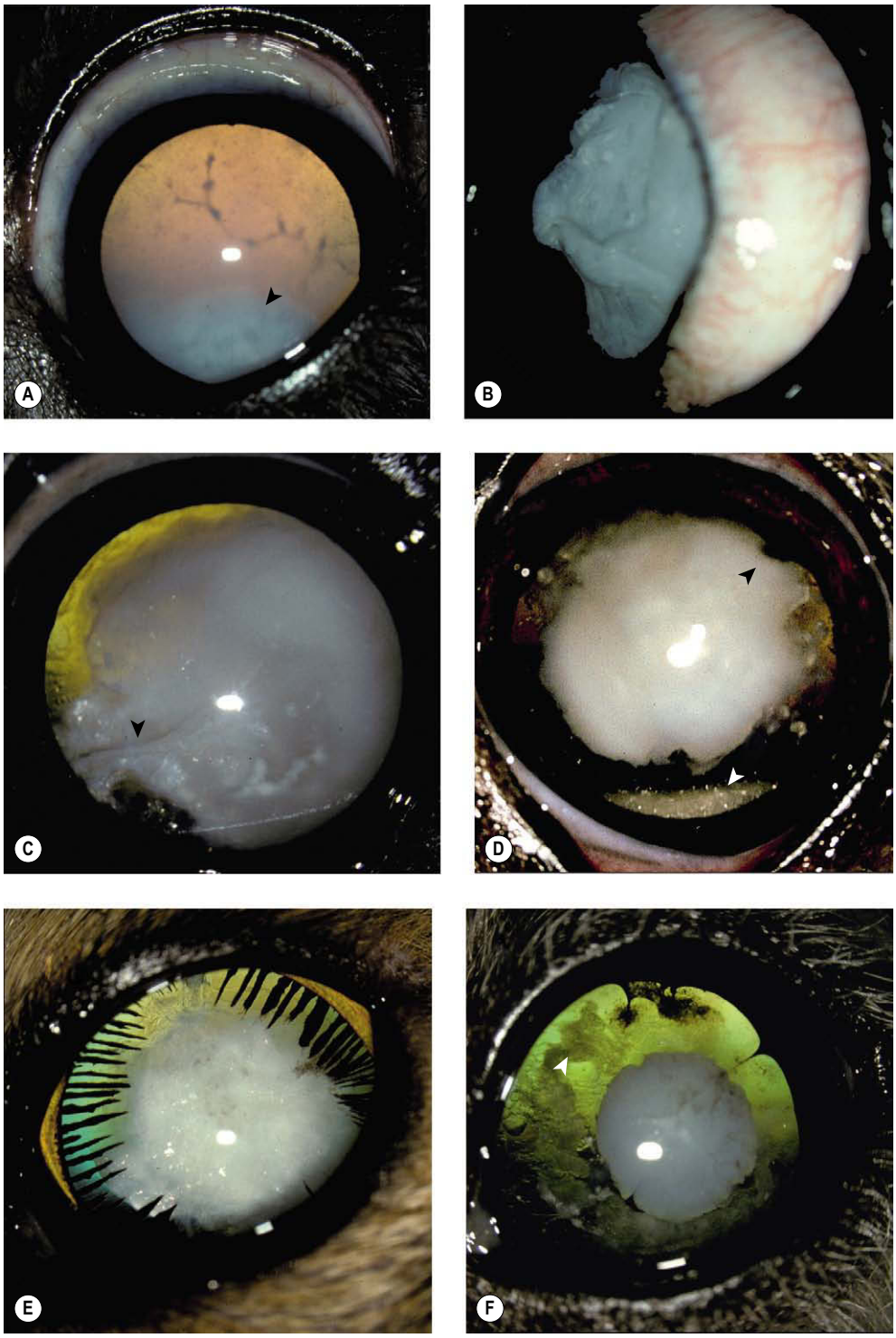


Figure 10.8 Morgagnian cataract and lens resorption, clinical. (A) Poodle, 4 years old: the dense nucleus (arrow) has settled inferiorly in the fluid cortex in this Morgagnian cataract. (B) Cocker Spaniel, 6 years old: viewing the lens from the side showing the severely wrinkled anterior lens capsule. This was the result of chronic loss of lens protein. (C) Cocker Spaniel, 2 years old: the orange tapetal reflection can be seen following lens resorption. A linear wrinkle in the lens capsule is also visible (arrow). (D) Bichon Frise, 10 years old: the dense nucleus is present with several areas of posterior synechiae (black arrow). Liquefied cortical material is present within the inferior capsule (white arrow). (E) DSH, 5 years old: the lens has reduced significantly in diameter and is surrounded circumferentially by stretched ciliary processes adhered to the lens capsule. (F) Bichon Frise, 6.5 years old: the small opaque nucleus remains axially. Fragments of cortical lens material (arrow) are trapped between the anterior and posterior lens capsule.

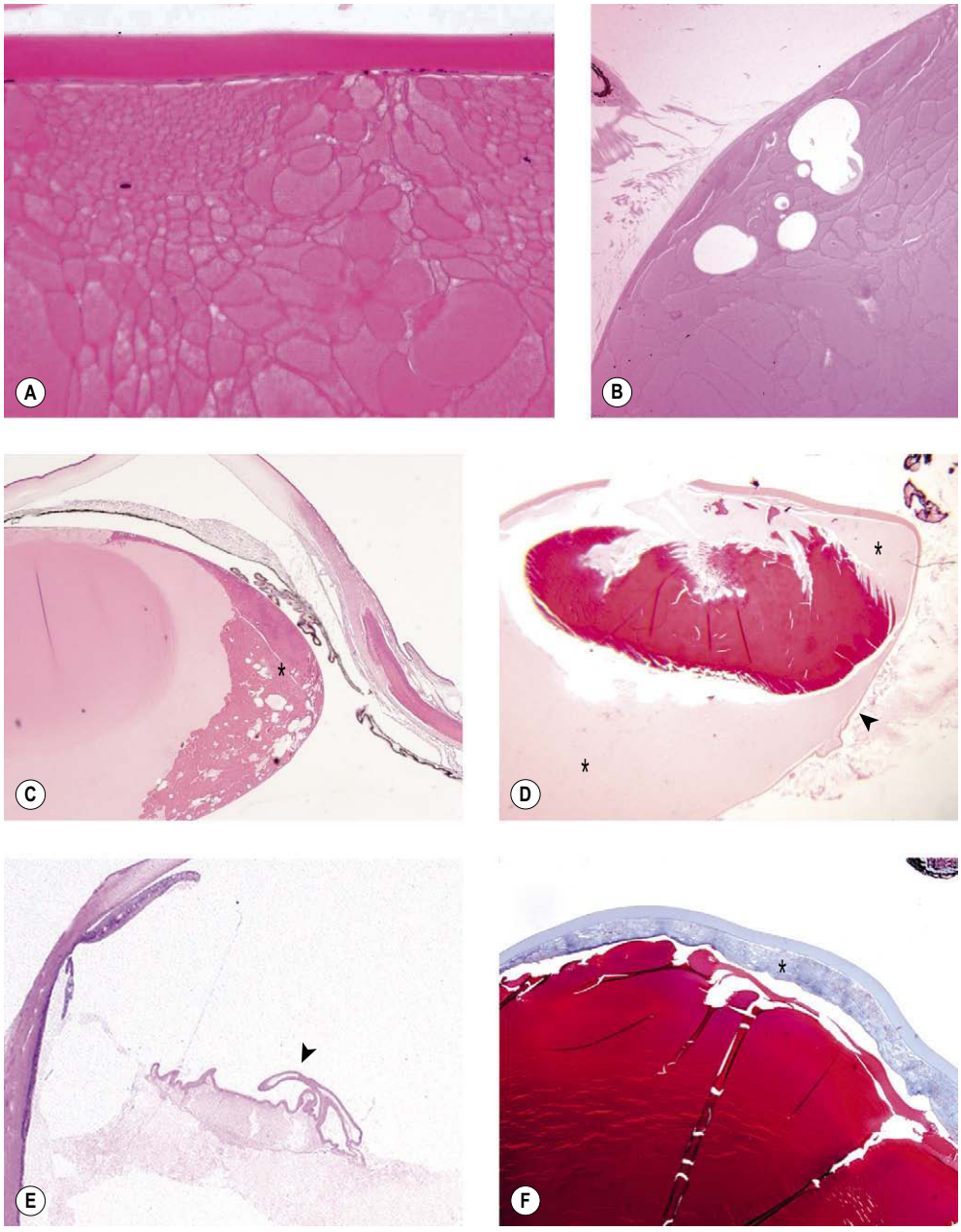


Figure 10.9 Classification of cataracts, pathology. (A) Photomicrograph showing cortical cataract, characterized by the presence of Morgagnian globules. (B) Bladder cells and Morgagnian globules in cortical cataract. A Morgagnian globule is a rounded lens fiber with no nucleus, and a bladder cell is a rounded fiber that contains a nucleus. (C) Photomicrograph of mature cataract showing extensive equatorial cortical pathology (*). (D) Hypermature Morgagnian cataract with wrinkling of the lens capsule (arrow) and remnants of lens nucleus floating in liquefied lens protein (*) within the capsule. (E) Low magnification photomicrograph showing the wrinkled lens capsule (arrow) after all the lens protein has been resorbed. (F) Hypermature cataract with extensive collagen-rich subcapsular cataract associated with spindle cell metaplasia of the lens epithelial cells (*).

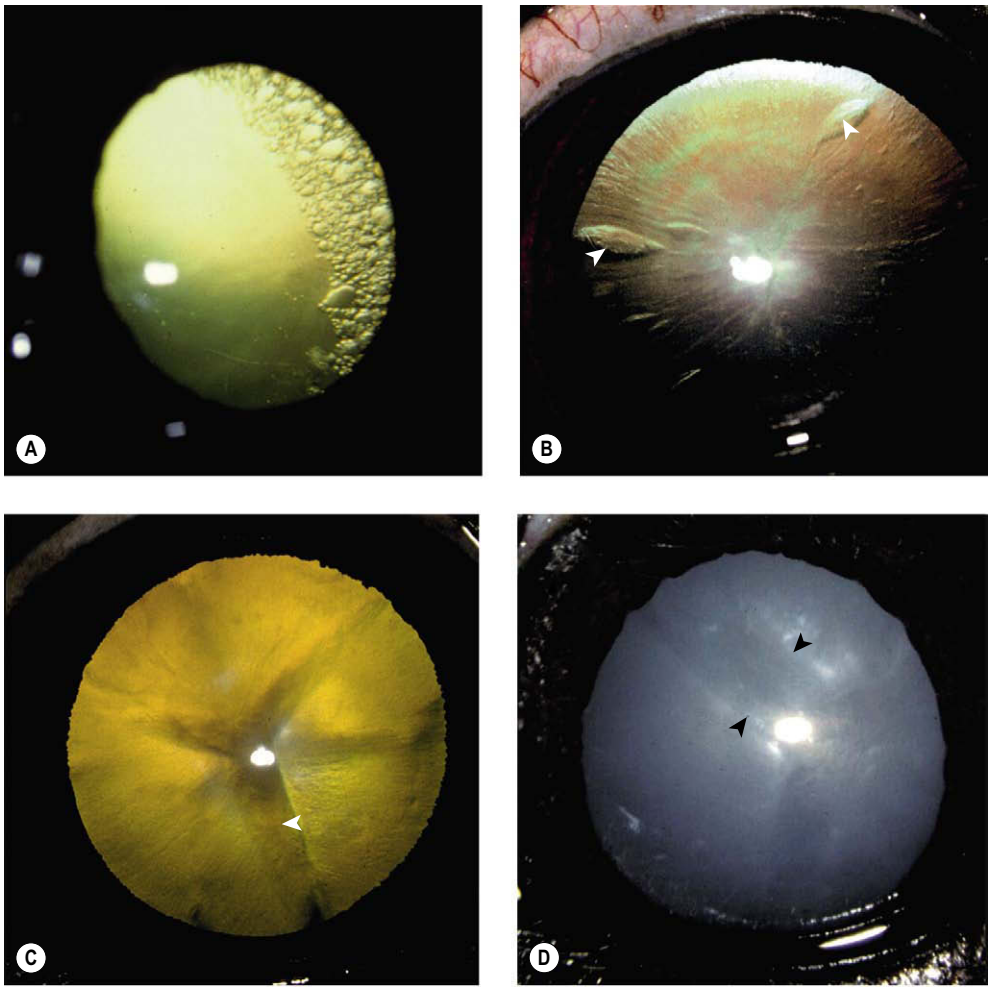


Figure 10.10 Diabetic cataract, clinical. (A) Keeshond, 9 years old: equatorial cortical water vacuoles were present circumferentially in both lenses. (B) Mixed Breed, 9 years old: equatorial water vacuoles were present. Fine radiations of cortical opacities and larger cortical water vacuoles (arrows) are present. (C) Rottweiler, 6 years old: this immature cataract has wide suture lines (arrow), which appear dark on retroillumination. Diffuse opacities throughout the overhydrated lens reduce the tapetal reflection. (D) Miniature Schnauzer, 9 years old: this intumescent lens is typical of the mature cataract seen in diabetes. The classical wide anterior cortical suture lines of an intumescent cataract are also observable (between arrows).

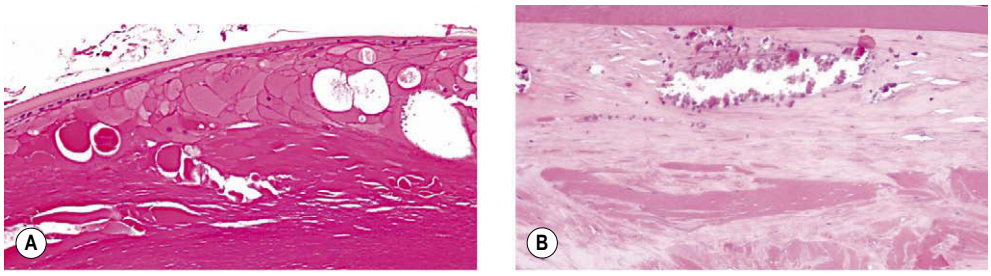


Figure 10.11 Histopathologic indicators of cataract. (A) Photomicrograph showing a canine lens with Morgagnian globules and bladder cells, two reliable histologic indicators of cataract. (B) Photomicrograph of a canine lens with cortical mineralization.

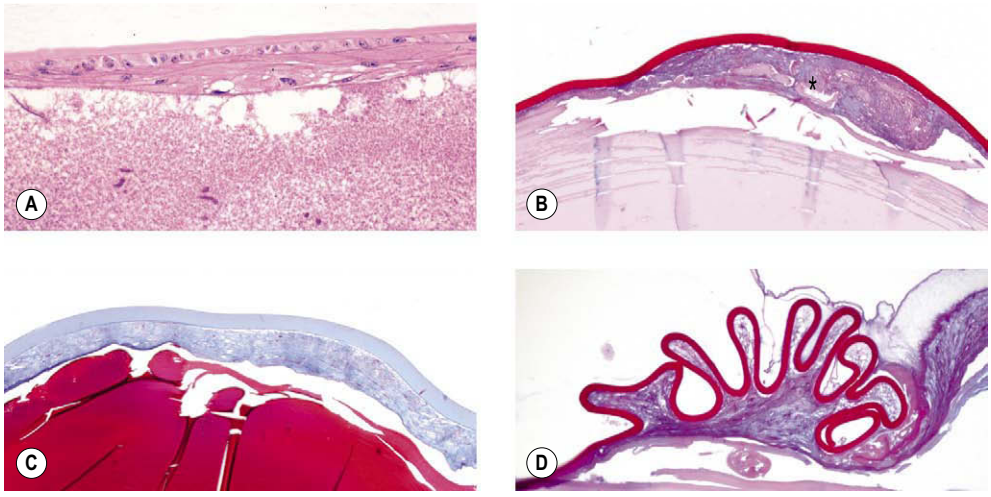


Figure 10.12 Subcapsular cataract, pathology. (A) Photomicrograph showing lens epithelial hyperplasia and metaplasia in subcapsular cataract. (B) Photomicrograph showing a collagenous subcapsular cataract (*) (Alcian blue PAS). (C) Photomicrograph of a trichrome-stained lens with a collagenous subcapsular cataract. (D) Hypermature cataract with a wrinkled lens capsule and a contractile subcapsular cataract.

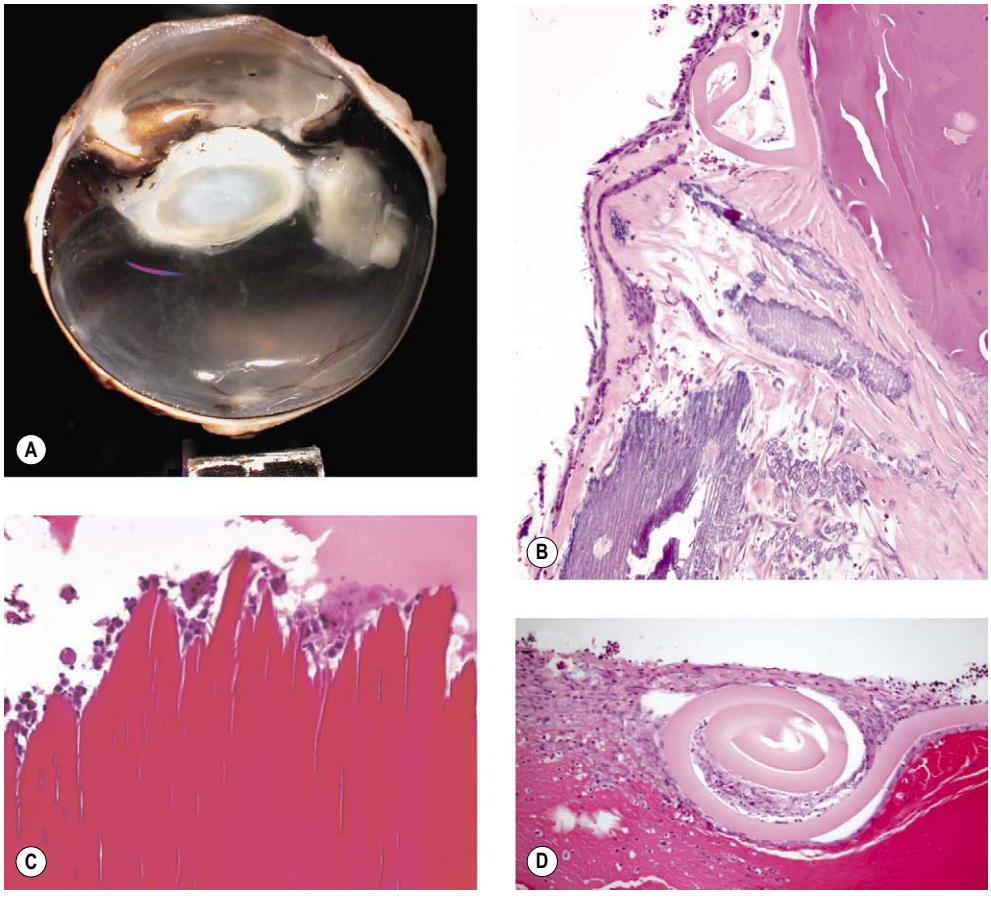


Figure 10.13 Lens capsule rupture, pathology. (A) Gross photograph of a canine globe with lens capsule rupture, release of lens protein and phacoclastic uveitis. (B) Mineralization within subcapsular cataract exposed by lens capsule rupture which is characterized by a coiled lens capsule. (C) Photomicrograph showing the exposed lens fibers after lens capsule rupture and consumption of lens protein by phagocyte proliferation. (D) Lens capsule rupture with scrolling of the lens capsule and proliferation of lens epithelial cells.

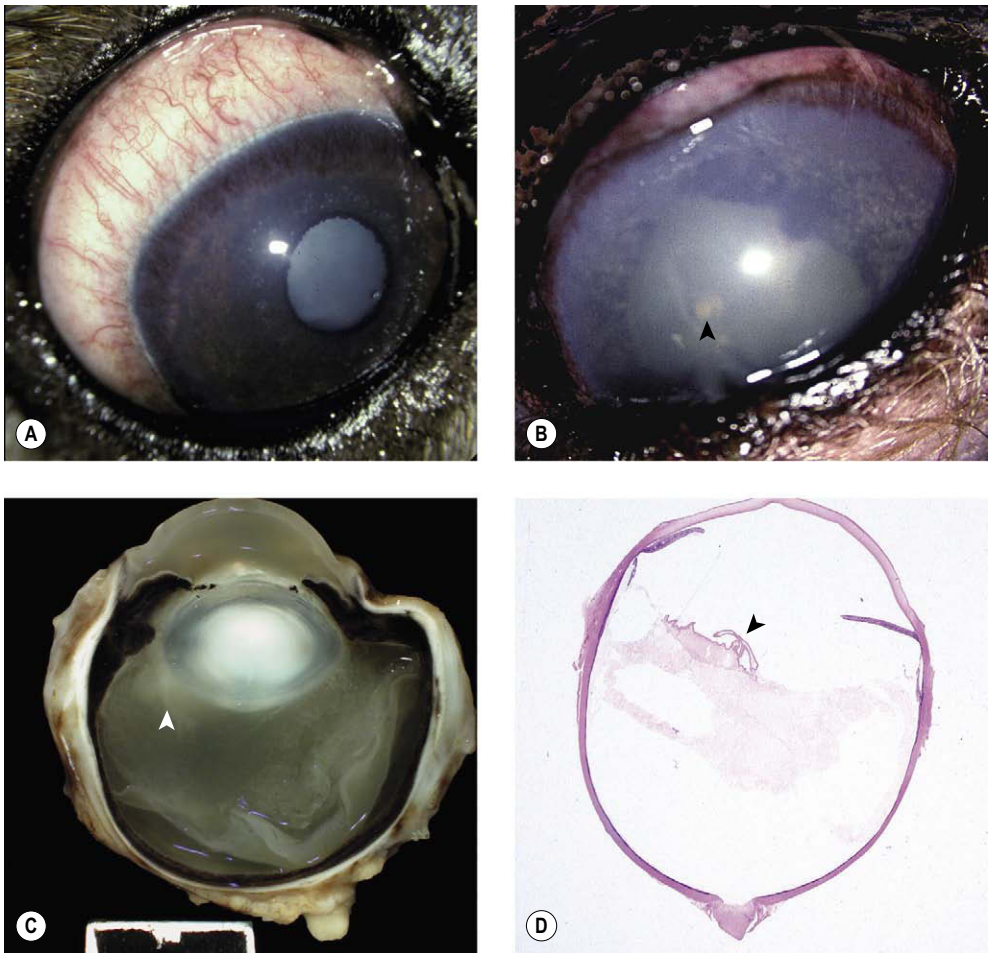


Figure 10.14 Phacolytic uveitis. (A) Cocker Spaniel, 13 months old: ectropion uvea is seen at the pupil margin. Deep limbal corneal vessels are present at the limbus. (B) Poodle, 9 years old: the lens is entrapped in the dilated pupil with irregular posterior synechiae. The iris has depigmented. Corneal edema and aqueous flare hinder the view of the keratic precipitates (arrow). (C) Gross photograph showing a canine globe with lens capsule still intact and protein exudates in the chambers of the globe (arrow). (D) Subgross photomicrograph from the same dog as 10.9(E) showing mild inflammation and the empty remains of the lens capsule in hypermature cataract (arrow).

- Lens rupture associated with rapidly progressive, intumescent diabetic cataract represents a special case, in which there is often a pronounced, macrophage-rich endophthalmitis associated with the explosive release of lens proteins (Fig. 10.15).

Septic implantation syndrome (see Ch. 5) (Fig. 10.16)

- A penetrating ocular injury causing lens capsule rupture with implantation of bacteria or, more rarely fungi, into the lens is a common occurrence in both cats and dogs
- Although impossible to prove in every case, this syndrome is most frequently caused by a cat scratch
  - There is often a latency period between the scratch and the onset of severe endophthalmitis
  - Because of the time that elapses between the original cat scratch and the clinically apparent endophthalmitis, the morphologic features of the disease include evidence of chronicity, such as:
    - Fibrosis and collagen deposition in association with the posterior synechiae
    - Development of a collagenous cyclitic membrane
- There is suppurative and histiocytic inflammation within the posterior chamber and within the ruptured lens
- Bacterial colonies or fungal hyphae are seen away from the inflammatory infiltrate, implanted within the lens substance
- Endophthalmitis is centered around the lens.

Phacoclastic uveitis in rabbits associated with the microsporidium, *Encephalitozoon cuniculi* (Fig. 10.17)

- This syndrome is characterized by a white inflammatory nodule adherent to the lens at the site of a lens capsule break and extending into the anterior chamber and anterior uvea
- Dwarf rabbits are over-represented
- Histologic features of *Encephalitozoon cuniculi*-associated phacoclastic uveitis
  - The inflammation is more confined and circumscribed than in septic implantation syndrome
  - There is a more prominent granulomatous component to the inflammation
  - *Encephalitozoon cuniculi* organisms may or may not be found. They are Gram-positive and a Gram-stain helps to demonstrate the organisms
- The mechanisms of disease transmission and pathogenesis have not been completely elucidated. Vertical transmission of the organism may be important in these cases, with lens infection occurring during lens development.

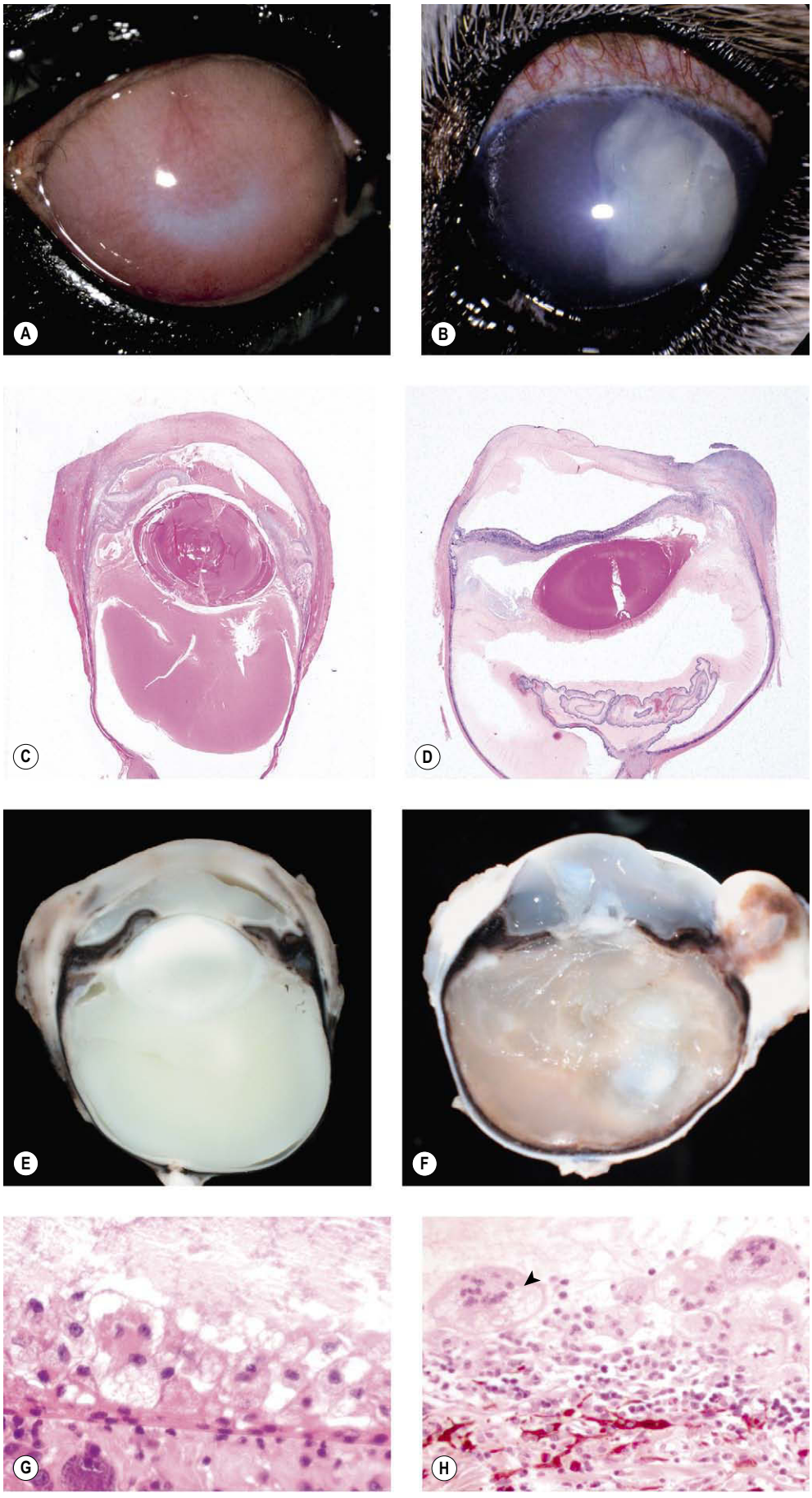


Figure 10.15 Diabetic cataract and phacoclastic uveitis. (A) Miniature Schnauzer, 7 years old: the posterior lens capsule was ruptured, resulting in a severe uveitis. The corneal edema and lipemic corneal vessels prevented visualization of the intraocular structures. (B) Samoyed, 10 years old: the anterior lens capsule has ruptured, extruding lens material into the anterior chamber. (C,D) Subgross photomicrographs showing canine globes with macrophage-rich uveitis and endophthalmitis in phacolytic diabetic cataract. (E,F) Gross photographs of eyes from two dogs with diabetic cataract and endophthalmitis. (G,H) Photomicrographs showing the detached retina (G) and the anterior surface of the iris (H) with a macrophage-rich infiltrate and multinucleate giant cells (arrow).

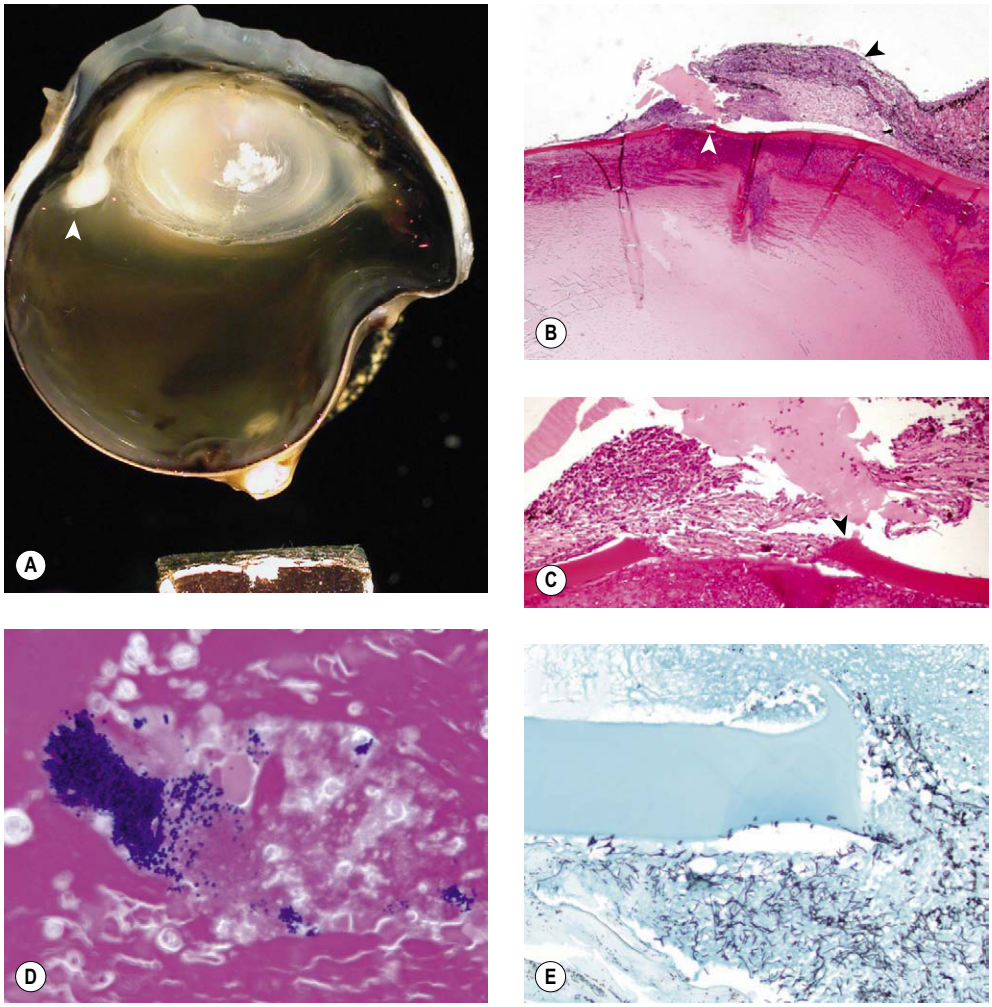


Figure 10.16 Septic implantation syndrome. (A) Gross photograph of dog eye showing a suppurative exudate (arrow) plastered between the lens capsule and the posterior iris in septic implantation syndrome. (B) Low magnification photomicrograph showing the relationship between the ruptured lens capsule (white arrow), the iris (black arrow) and the crystalline lens. (C) Higher magnification showing the lens capsule rupture and the ragged edge of the capsule (arrow) infiltrated by neutrophils. (D) High magnification photomicrograph showing Gram-positive bacterial cocci embedded in the lens away from the suppurative exudates, typical of septic implantation syndrome (Gram stain). (E) High magnification showing long filamentous bacteria in a cat with septic implantation syndrome.

Comparative Comments

Phacolytic uveitis, generally referred to in humans as phacoantigenic endophthalmitis, or lens-related uveitis, is a similar pathologic entity to that described in other species and is seen commonly in phakic eyes with sympathetic ophthalmia.

THE LENS EPITHELIUM AND ITS ROLE IN DISEASE AFTER LENS CAPSULE RUPTURE (Fig. 10.18)

Following spontaneous lens capsule rupture, chronic cataract, or following cataract surgery, remaining lens epithelial cells undergo a predictable series of changes which can lead to serious complications.

- Spindle cell metaplasia, forming cells that express smooth muscle actin that are typical of myofibroblastic mesenchymal cells
- Proliferation of remaining epithelial cells and migration of metaplastic cells within the lens capsule
  - In humans, the migration of lens epithelial cells is confined to the lens capsule, but this is not the case in dogs and cats
  - Together with mesenchymal transformation, this is a major cause of posterior capsular opacification following cataract surgery in humans and animals. Complications of cataract surgery are discussed in detail in Chapter 4
- Migration of metaplastic lens epithelial cells to cover the inner aspect of the uvea, lining the globe
- Potential, vision-threatening consequences of the migration of metaplastic lens epithelial cells out of the lens capsule include:
  - Synechiae formation
  - Traction leading to retinal detachment
  - Glaucoma due to angle closure or pupillary block
  - Proliferative membranes in the posterior segment
- Malignant transformation causing spindle cell variant post-traumatic ocular sarcoma in cats (see Ch. 5) (Fig. 10.19)
  - After a latency period which averages 7 years following traumatic lens capsule rupture, lens epithelial cells may undergo transformation into malignant spindle cells
  - The malignant cells extend around the interior of the globe and may infiltrate into the sclera, optic nerve, and peripheral nerve tissue
  - Malignant cells often continue to secrete a thick, lens capsule-like basement membrane and may also continue to express alpha A crystallin protein.

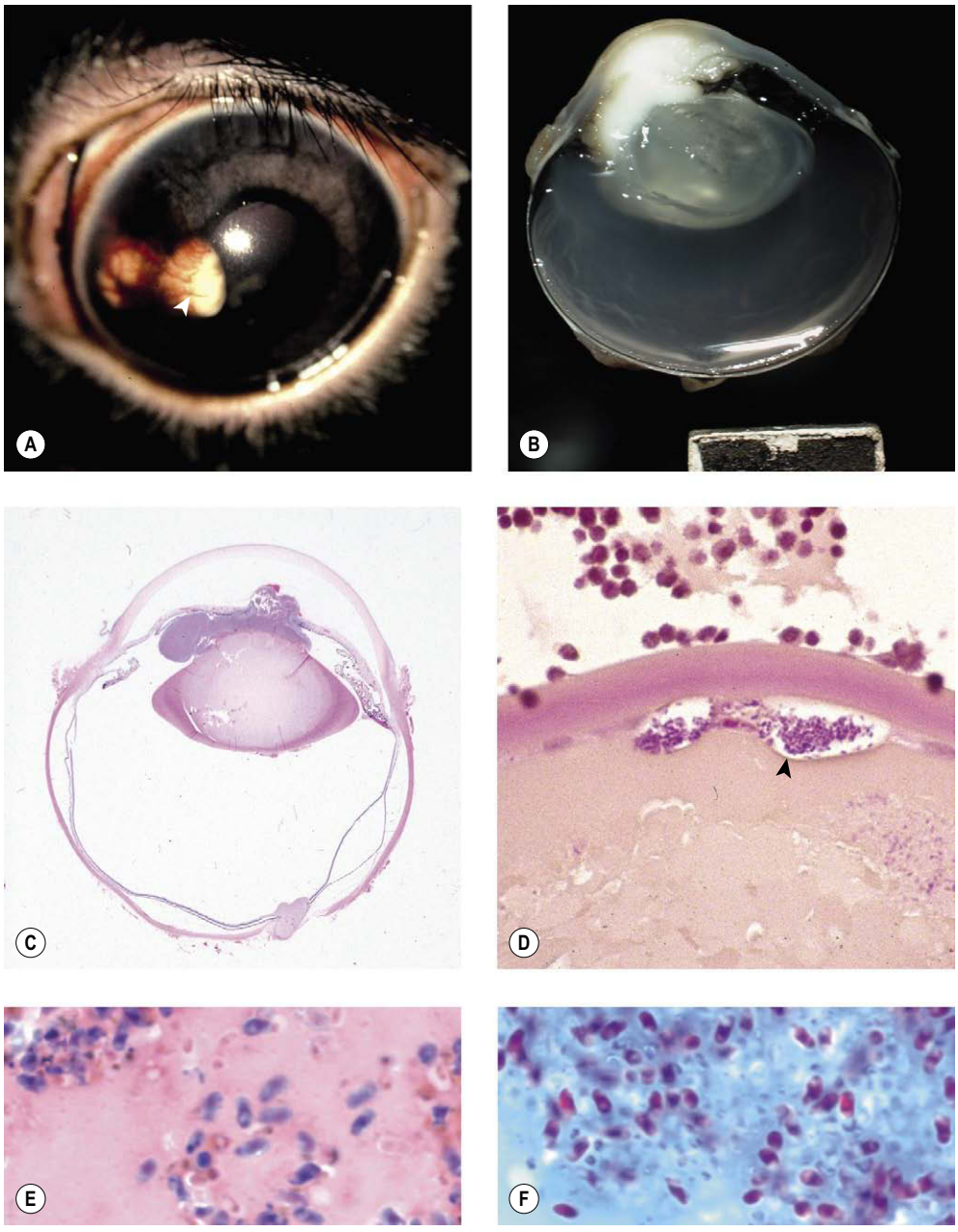


Figure 10.17 *Encephalitozoon cuniculi* and lenticular rupture in rabbits. (A) Dwarf cross, 1 year old: two raised granulomatous, vascularized masses (arrow) originate in the iris and extend into the anterior chamber. A nasal anterior cortical cataract cannot be viewed in this photograph. (B) Gross photograph showing a highly cellular exudate hugging the anterior capsule of the lens. This pattern is typical of *Encephalitozoon cuniculi*-induced inflammation. (C) Subgross photomicrograph showing a cellular exudate between the anterior lens capsule and the iris. (D) Photomicrograph showing the anterior lens with a cluster of protozoal organisms within the lens (arrow). (E,F) *Encephalitozoon cuniculi* organisms in the lens (Gram stain (E) and acid-fast stain (F)).

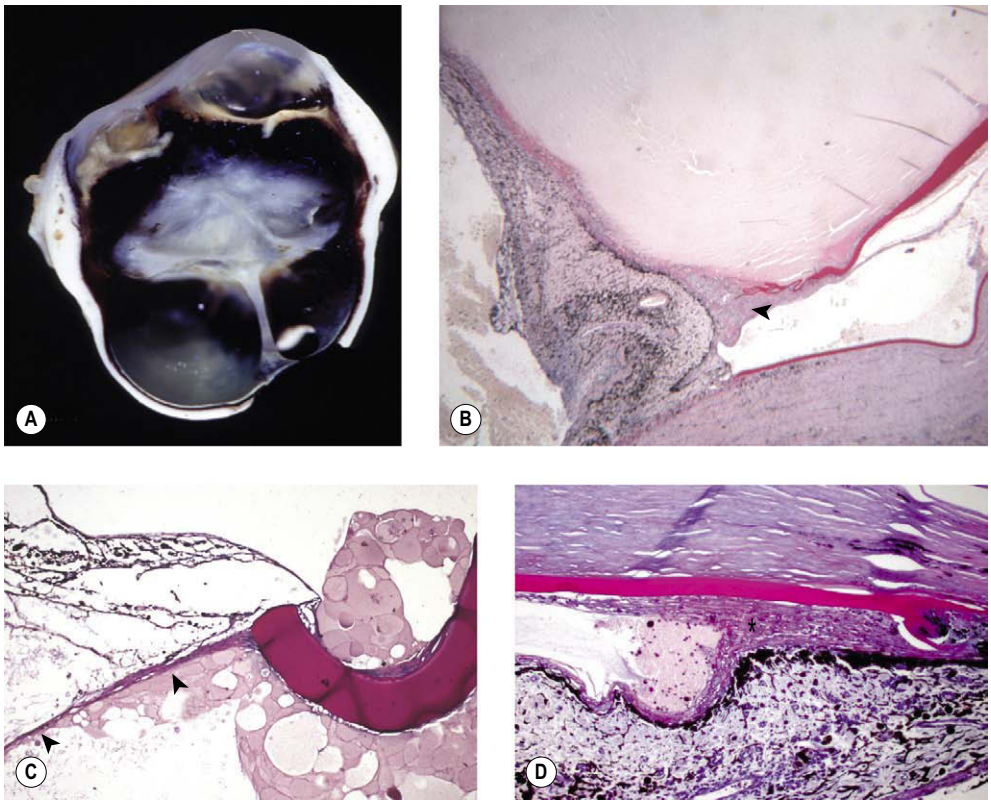


Figure 10.18 Proliferation of lens epithelial cells after traumatic lens capsule rupture. (A) Gross photograph of a traumatized feline globe showing a hypermature cataract. The retinal remnants and the uvea are distorted because of proliferating lens epithelial cells. (B) Photomicrograph showing lens capsule rupture and proliferating lens epithelial cells (arrow) spreading over the iris and iridocorneal angle. (C) Higher magnification photomicrograph showing the ruptured end of a canine lens capsule. A membrane composed of lens epithelial cells, accompanied by PAS-staining basement membrane matrix (arrows), extends from the margin of the lens capsule. Such a membrane will contribute to retinal detachment or synechia. (D) Photomicrograph of a canine anterior chamber with a thick membrane of proliferative and migrating lens epithelial cells (*) causing anterior synechia.

LENS LUXATION

- Lens luxation is the separation of the lens from its zonular ligament moorings (Figs 10.20, 10.21)
- The position of a highly mobile luxated lens can change rapidly, before the observer's eye.

Subluxation

Partial dislocation of the lens which, although somewhat displaced, remains within the patella fossa on the anterior vitreous face.

Anterior luxation

The dislocated lens lies partly or entirely within the anterior chamber.

Posterior luxation

The dislocated lens falls back into the vitreous, implying degeneration or disruption of the anterior vitreous.

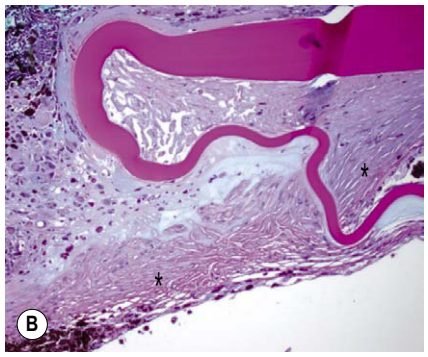
Detecting pre-existing lens luxation in the enucleated globe

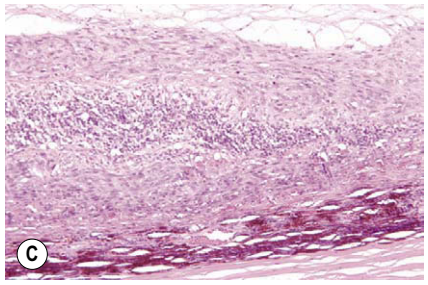
- Detecting lens luxation can be problematic because the lens is commonly displaced artifactually during cutting and processing of the globe
- The best way to detect a pathological lens luxation is to read the history carefully because the ophthalmologic exam is most likely to be accurate
- Morphologic features of lens luxation apparent on the gross examination of the globe include:
  - Lens out of position and free within the globe
  - Liquid vitreous body, often with strands across the front or attached to the free lens
- Morphologic features of lens luxation apparent on histopathology include:
  - An angular, posterior bend in the profile of the iris ('dogleg' iris)
  - Atrophy of the pars plicata of the ciliary body
  - Attenuation of the corneal endothelium secondary to touch by the luxated lens.

Vision-threatening consequences of lens luxation (Fig. 10.22)

- Physical contact between the luxated lens and the corneal endothelial cells results in attenuation of the endothelium or formation of a retro-corneal membrane
  - Loss of function of the central or paraxial corneal endothelium may result in corneal edema
  - Corneal edema, in turn, may lead to:
    - Bullous keratopathy and corneal ulceration
    - Secondary infectious keratitis
    - Collagenolysis with corneal perforation
- Entrapment of the lens in the anterior chamber causing angle closure and/or pupillary block with secondary glaucoma
- Posterior synechiae leading to pupil block, iris bombé and glaucoma
- Anterior vitreous prolapse contributing to retinal detachment or pupil-block and secondary glaucoma.







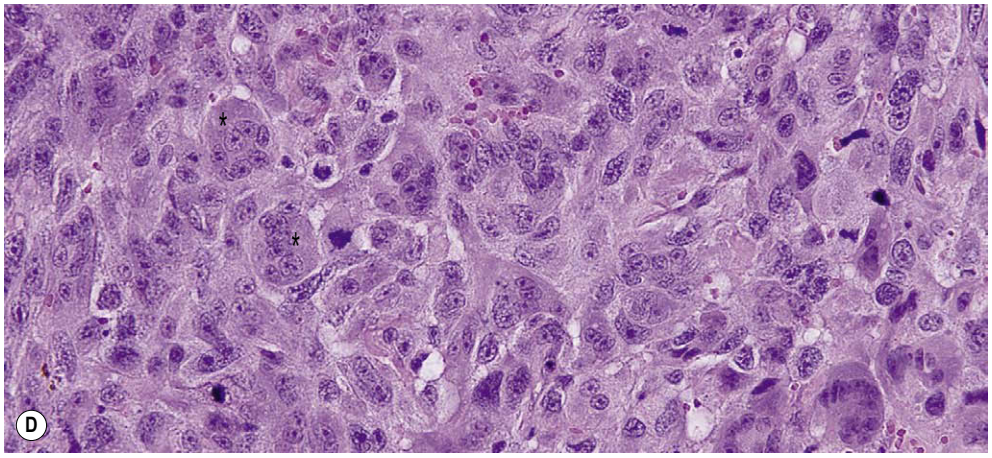


Figure 10.19 Feline post-traumatic ocular sarcoma. (A) Gross photograph of a globe with feline post-traumatic ocular sarcoma, spindle cell variant. (B) Photomicrograph of the ruptured lens capsule from a traumatized cat eye showing neoplastic cells of lens epithelial origin (*). (C) Photomicrograph showing a neoplastic membrane on the inner surface of the choroid in a pattern typical of post-traumatic sarcoma. (D) Photomicrograph showing neoplastic spindle cells in feline post-traumatic sarcoma and associated multinucleated giant cells (*), which are seen in some post-traumatic ocular sarcomas.

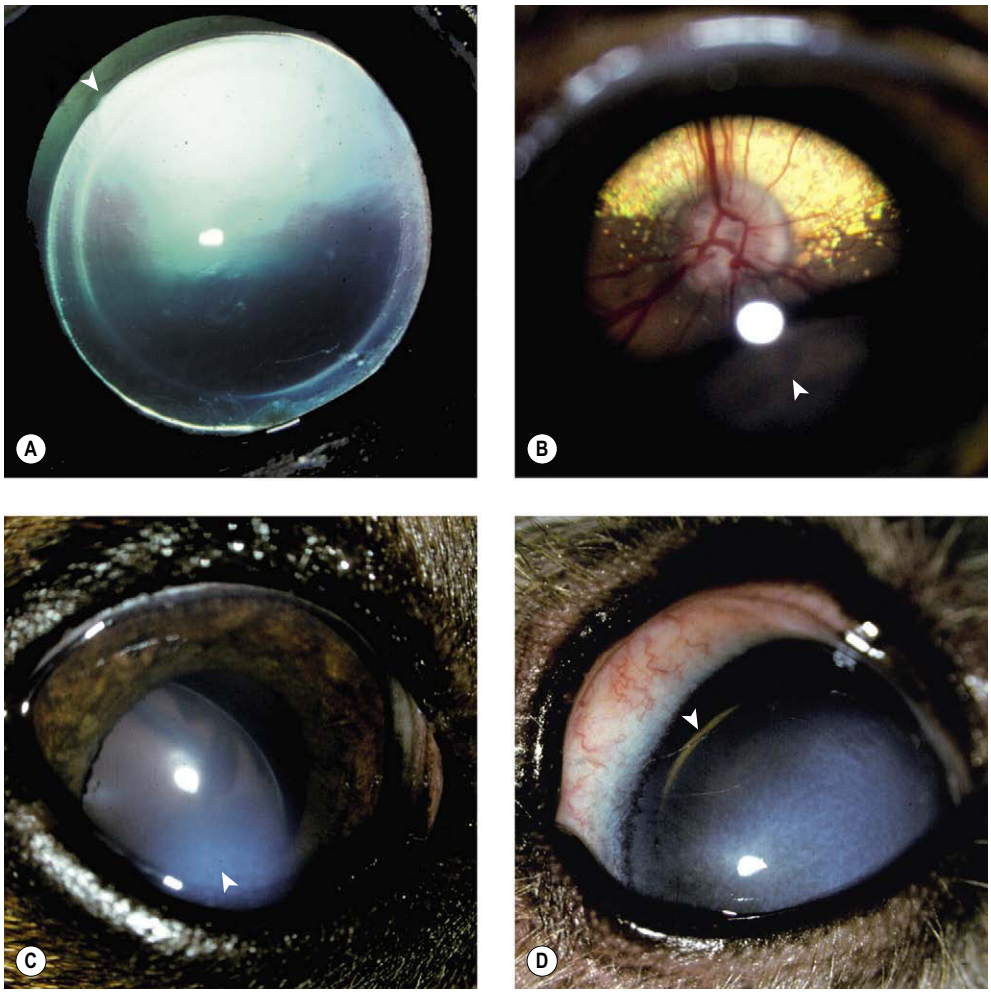


Figure 10.20 Lens luxation, clinical. (A) Petit Basset Griffon Vendéen, 4 years old: an aphakic crescent (arrow) and the entire equator of the lens can be seen in this subluxated lens. (B) Brittany Spaniel, 7 years old: the optic disc can be easily seen through the dilated pupil and over the posterior luxated lens (arrow). (C) Dachshund, 6 years old: the lens is tilted and subluxated with the nasal aspect of the lens contacting the corneal endothelium (arrow) and the temporal lens still posterior to the iris. (D) Tibetan Terrier, 6 years old: the entire lens is luxated into the anterior chamber resulting in corneal edema. The equator of the lens can be seen superiorly (arrow).

Causes of secondary lens luxation include

- Chronic intraocular inflammation leading to degradation of the lens zonules
- Chronic glaucoma with enlargement of the globe
- Long-standing, hypermature cataract with lens shrinkage and phacolytic uveitis
- Senile degeneration of the zonular ligaments in elderly animals
- Traumatic disruption of the lens zonules
  - In domestic animals traumatic lens luxation is seldom recognized in isolation, and is likely to be accompanied by other signs of ocular trauma, such as intraocular hemorrhage.

Breed-related zonular ligament dysplasia as a risk factor for canine primary lens luxation (Fig. 10.23)

- Primary lens luxation is seen as a primary condition, presumably with a hereditary basis, in several dog breeds including terrier breeds, Tibetan Terriers and Shar Peis. Primary lens luxation is also encountered sporadically in other breeds and in other species
- Morphologic features that are useful in the histologic diagnosis of zonular ligament dysplasia include:
  - Affected animals will have solid sheets of acellular, eosinophilic protein tightly adherent to the non-pigmented epithelium over segments of the ciliary body
    - The abnormality is discontinuous so a careful evaluation of all available ciliary epithelium is needed to rule out zonular ligament protein dysplasia
    - Thickening of the native zonular ligaments is a non-specific change which can be distinguished from zonular ligament dysplasia because it is not tightly adherent to the epithelium
  - When viewed with enhanced contrast, these protein deposits have a complex cross-pattern of laminations
  - The abnormal protein stains intensely with PAS and, in contrast to normal zonular ligaments, stains blue with trichrome indicating increased collagen and does not stain black with an elastin stain
- Affected dogs have bilateral ocular involvement at a young age
- Other systemic connective tissue abnormalities, as seen in humans with lens luxation related to Marfan syndrome, have not been identified in affected dogs
  - In humans with Marfan syndrome, fibrillin gene mutations have been identified
  - Mutations in the fibrillin gene have not been identified in canine breeds with primary lens luxation.

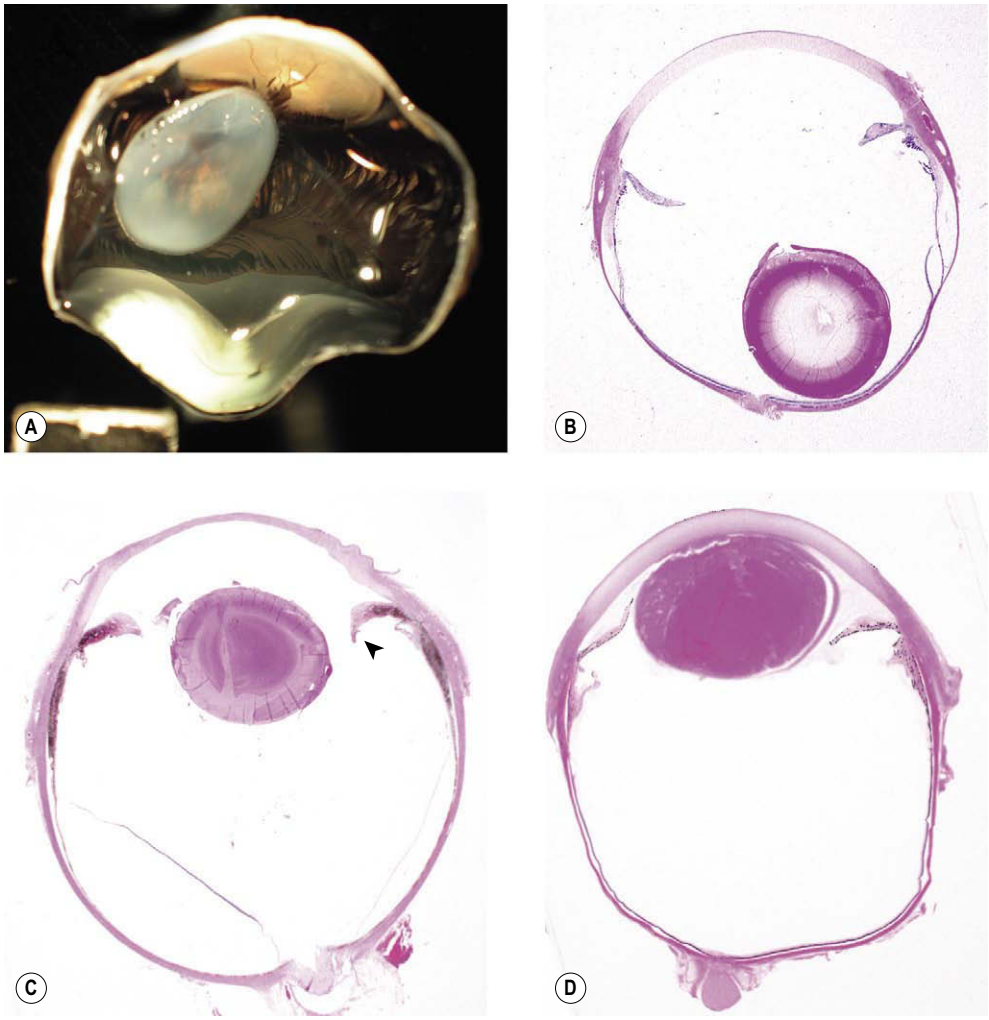


Figure 10.21 Morphologic features indicative of lens luxation. (A) Gross photograph of a dog eye with displacement of the lens. The pathologist is best able to evaluate the lens position while grossing the eye. (B) Subgross photomicrograph showing the lens in the vitreous. This change has a high probability of being an artifact of handling. (C) Subgross photomicrograph showing the lens displaced and the papillary margin of the iris bent around the lens equator (arrow). This is a hint that the lens displacement is pathologic. (D) Subgross photomicrograph showing the lens clearly in the anterior chamber.

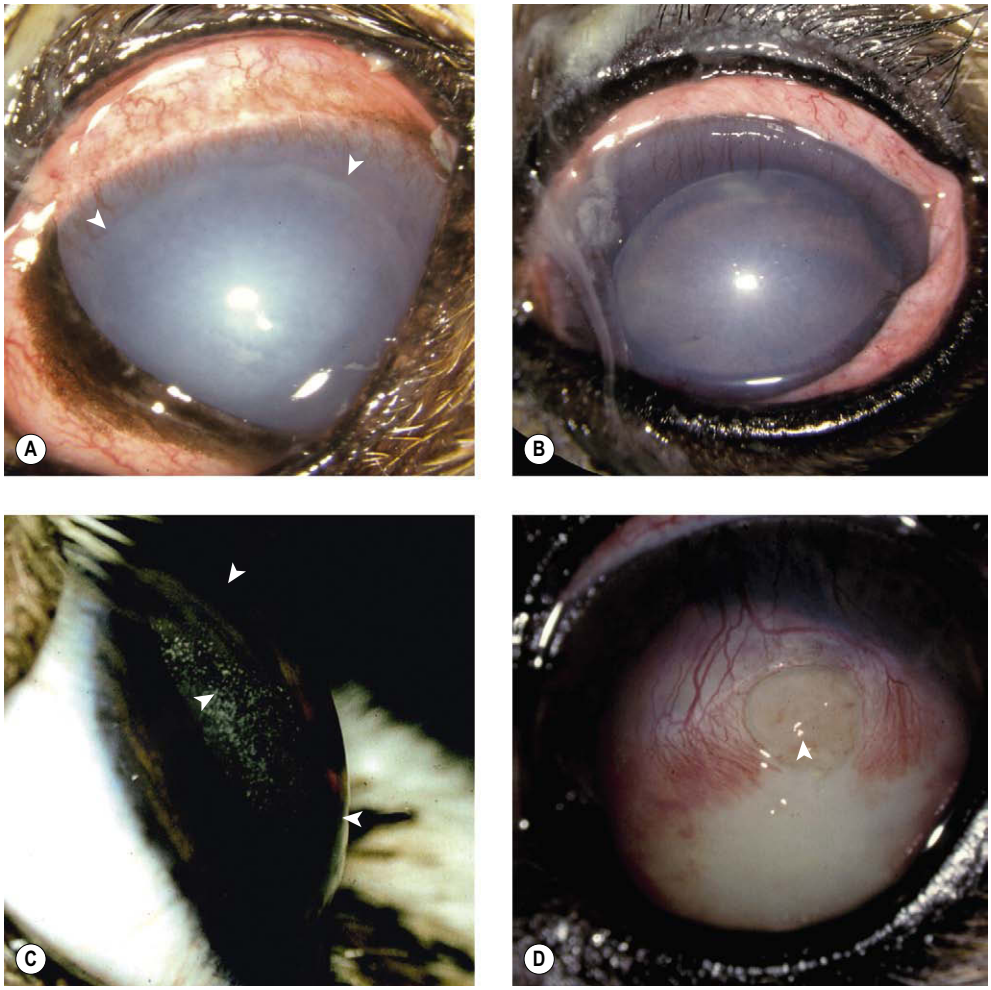


Figure 10.22 Consequences of lens luxation, clinical. (A) Terrier cross, 14 years old: the lens equator (arrows) can be seen in the anterior chamber. Glaucoma and keratitis resulted from the anterior lens luxation. (B) Pomeranian, 7 years old: the lens was luxated into the anterior chamber. Anterior uveitis was apparent on ocular examination. (C) Mixed Breed, 8 years old: the lens was subluxated posteriorly. Two arrows delineate the corneal curvature. The central arrow at 9:00 points to the asteroid hyalosis and prolapsed vitreous in the anterior chamber. (D) Yorkshire Terrier, 11 years old: the mature cataract has luxated into the anterior chamber resulting in endotheliitis and keratitis. An elevated descemetocele has formed at the arrow.

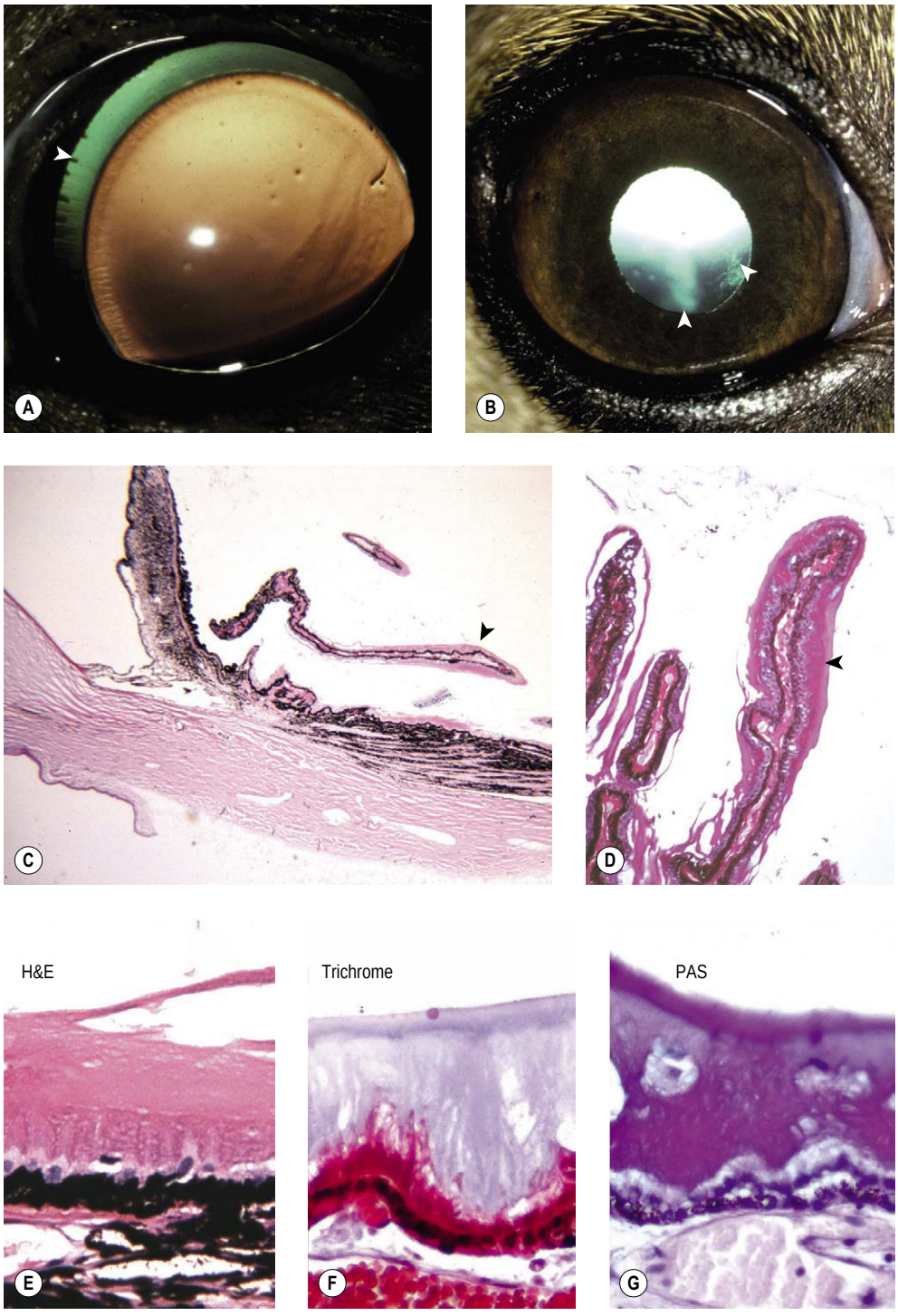


Figure 10.23 Lens luxation associated with zonular ligament dysplasia. (A) Chinese Shar-Pei, 8 years old: this lens is subluxated posterior and inferior. Ciliary processes (arrow) and fine zonular fibers can be seen at the aphakic crescent. (B) Parson Russell Terrier, 4 years old: this normotensive eye had a deep anterior chamber due to a posterior lens luxation. Zonular fibers are seen at the pupil margin (arrows). (C) Low magnification photomicrograph showing the ciliary body of a Jack Russell Terrier with lens luxation and a region of dysplastic zonular ligament protein (arrow). (D) Higher magnification of the same dog eye as (C) stained with PAS showing another region on the pars plicata with an acellular carpet of dysplastic zonular ligament protein (arrow). (E–G) High magnification photomicrographs showing the morphologic features of dysplastic zonular ligament protein and its staining characteristics. (E) The features with an H&E stain. The acellular material shows a complex crosshatched lamellar pattern. (F) The material is trichrome-positive, unlike the native zonular ligament. (G) The dysplastic protein is strongly PAS-positive, as is the native zonular ligament protein.

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Chapter 11

The Retina

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GENERAL CONSIDERATIONS

Normal anatomy (Fig. 11.1)

The retina extends from the optic nerve head to the ora ciliaris retinae, where it merges with the two layers of ciliary epithelium. Conventionally, the retina is considered to be a highly organized extension of the forebrain that consists of 10 layers of specialized cells.

When considering these layers, 'inner' refers to structures closer to the vitreous/center of the globe, while 'outer' refers to structures that are closer to the sclera.

The neurosensory retina refers to the inner nine layers, exclusive of the outermost layer, the retinal pigment epithelium (RPE). From inner to outer these layers consist of:

The neurosensory retina

The inner limiting membrane

- The basal lamina separating the neural retina from the vitreous body
- Formed by fused inner processes of adjacent Müller cells.

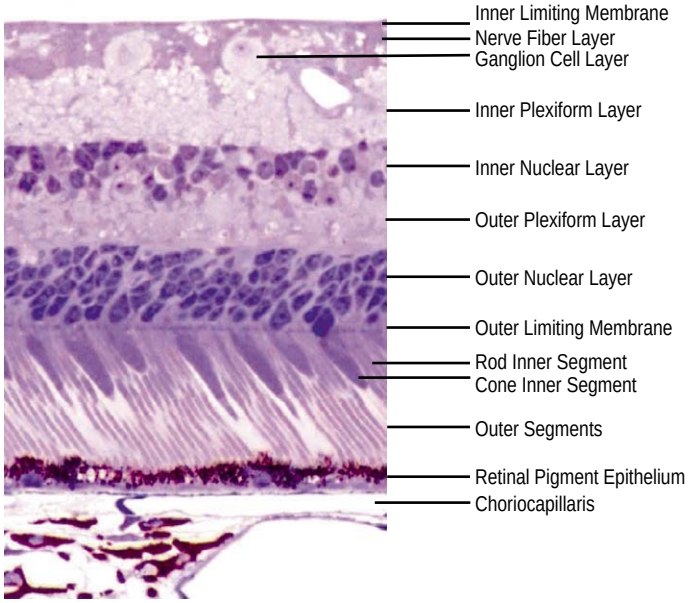


Figure 11.1 Normal retina. Photomicrograph of a plastic section of a perfusion-fixed primate retina with the various layers as labeled.

The optic nerve fiber layer

- Contains the axons of the ganglion cells supported by Müller cell and other astrocyte processes
- Thickest near the optic nerve head and thinnest at the fovea (where present), or area centralis.

The ganglion cell layer

- Retinal ganglion cells (RGCs) are unevenly distributed throughout the retina, and their absolute numbers and relative density vary from species to species
- Although different types of RGCs may be classified based on their size or physiological properties, they all have abundant cytoplasm containing Nissl substance
- Ganglion cell density is greatest in an area near the macula (primate) or area centralis (dog or cat) that is known as the visual streak
- A greater density of ganglion cells is typically observed in eyes adapted for best vision in bright daylight or for maximal visual acuity, and there are fewer in eyes adapted for vision in dim light
- A variable number of displaced amacrine cells may be present within the ganglion cell layer.

The inner plexiform layer

- The synapses between the RGCs and the neurons of the inner nuclear layer, i.e. amacrine and bipolar cells.

The inner nuclear layer

- Contains the cell bodies of the following cell types:
  - Müller cells
    - The retinal equivalent of glial cells
    - The Müller cell processes extend from the innermost retina to the outer limiting membrane, supporting and nourishing all of the constituent cells and, at least in some species, forming a plexus of processes around intraretinal blood vessels
  - Three general classes of neurons that are responsible for connections between photoreceptors and RGCs:
    - Amacrine cells in the inner aspect of the inner nuclear layer
      - Amacrine cells have more abundant cytoplasm than bipolar cells
      - A population of displaced amacrine cells also exists in the RGC layer
    - Bipolar cells lie in the middle of this layer (along with Müller cell bodies)
    - Horizontal cells lie in the outer aspect of the inner nuclear layer
      - Horizontal cell nuclei are large and have single, prominent nucleoli.

The outer plexiform layer

- Represents the synapses between the photoreceptor cells, and the dendrites of horizontal and bipolar cells that lie in the inner nuclear layer
  - Cone synaptic terminals consist of wide pedicles
  - rod synaptic terminals consist of small spherules
- Is thinner than the inner plexiform layer.

The outer nuclear layer

- Contains the nuclei of the photoreceptor cells (rods and cones)

- Species with eyes adapted for vision in dim light generally have a relatively rod-rich retina and, therefore, a relatively thick outer nuclear layer, e.g. consisting of about 20 rows of nuclei in the cat, whereas species adapted for vision in bright light and those adapted for maximum visual acuity, typically have a thinner outer nuclear layer
- This layer is thinner in the periphery of the retina, where photoreceptor density is lowest
- Cone nuclei are slightly larger and lighter staining than rod nuclei and, usually, are positioned adjacent to the outer limiting membrane.

The outer limiting membrane

- The outer limiting membrane is not a physical layer but consists of a continuum of tight junctions connecting the cell membranes of photoreceptor cells and Müller cells
- The tight junctions of the outer limiting membrane along with tight junctions at the apices of the RPE cells are the anatomic features that delineate the sub-retinal space
- The subretinal space is the potential space between the photoreceptor outer segments and the retinal pigment epithelial cells (RPE) and, since it is enclosed by tight junctions, it normally only contains secreted substances, within the inter-photoreceptor matrix. This is an important factor in maintaining organization of the outer retina and preserving the intimate contact between the neural retina and the RPE.

The photoreceptor layer

The photoreceptor layer is composed of:

- Photoreceptor inner segments
  - Cytoplasmic component of the photoreceptor cell packed with mitochondria and rough endoplasmic reticulum
  - Photoreceptor cells are among the most metabolically active cells in the body, both in terms of oxygen consumption and protein production
  - Rod and cone photoreceptors can be distinguished by the shape of their inner segments
  - The central retina, superior and temporal to the optic nerve, is a relatively cone-rich zone in many species. Furthermore, many avian, reptile and primate species have foveae, regions that are largely devoid of rods
- Photoreceptor outer segments
  - The site of phototransduction
  - Both rod and cone outer segments are made up of parallel stacked membranes containing visual pigments that consist of the appropriate opsin proteins charged with photosensitive vitamin A-derivative, retinal
  - The photoreceptor outer segments are complex modifications of cilia and maintain some of the structural features of cilia at their junction with the inner segments.

The retinal pigment epithelium (RPE)

- The RPE is a monolayer of cells that is derived from the outer layer of neuroepithelium of the optic cup, and is continuous with the outer pigmented epithelium of the ciliary body at the ora ciliaris retinae
- Apical microvillous processes of each RPE cell invest the outer segments of numerous photoreceptors
- Although typically densely pigmented, RPE cells are non-pigmented in the area that overlies the tapetum (see Ch. 9), losing their melanosomes by a process of autophagocytosis concurrent with tapetal development within the choroid
- Together, the basement membranes of the RPE and adjacent choriocapillaris form the structure known as 'Bruch's membrane'
- The RPE has a number of important roles in maintaining the functional integrity of the overlying neurosensory retina:
  - Oxygen and nutrients for the outer retina are transported through the RPE from the choriocapillaris of the choroid
  - The RPE serves to phagocytose the outermost portion of the photoreceptor outer segment that is cyclically shed, in a continuous process of outer segment renewal
  - 'Spent' retinol from visual pigment cycles from the outer segment to the RPE and back. The RPE cell essentially regenerates the retinal which is a component of visual pigment, so that it is ready to function in the process of phototransduction again
  - The melanin pigment of the RPE absorbs light and therefore reduces intraocular light scatter and glare
  - Tight junctions between cells of the RPE help maintain the blood-retinal barrier, and delineate the subretinal space
  - The RPE limits photo-oxidative damage that is associated with the high levels of oxygen, light and free-radicals in the outer retina, by a number of antioxidant mechanisms.

Retinal blood vessels (Fig. 11.2i,ii)

- Retinal blood vessels have tight junctions and function as part of the blood-retinal barrier
- Where present, retinal blood vessels are found within the nerve fiber, ganglion cell and inner plexiform layers of the inner retina; capillaries are also present in the inner nuclear layer
- The pattern of retinal blood vessels is highly variable between different species:
  - Holangiotic, with blood vessels distributed throughout most of the neurosensory retina, supplying the inner retina only.
    - Carnivores, primates, even-toed ungulates, most rodents
  - Paurangiotic, with blood vessels limited to the retina immediately adjacent to the optic nerve head and the rest of the retina being avascular
    - Horses and other odd-toed ungulates
    - Guinea pigs and some rodents
  - Merangiotic, with retinal blood vessels confined to a linear horizontal streak on both sides of the optic disc, accompanying streaks of myelinated nerve fibers
    - Lagomorphs
  - Anangiotic
    - Other vertebrate groups have a variety of vascular structures within the vitreous adjacent to the retina, but only mammals have true intra-retinal vasculature
    - Birds have no retinal vessels but they have a complex vascular structure, the pecten, which extends into the vitreous from the optic nerve head.

Comparative Comments

- The normal anatomy of the human retina resembles in most respects that of other vertebrate species
- The human macula, a feature shared with most other primates, represents a refinement of the *area centralis* of other mammals. A xanthophyll pigment gives the macula a yellow appearance clinically and on gross examination, but the xanthophyll dissolves during tissue processing and is not present in histologic sections. The macula is the portion of the retina that is responsible for the high degree of visual acuity in primates. In its histologic and

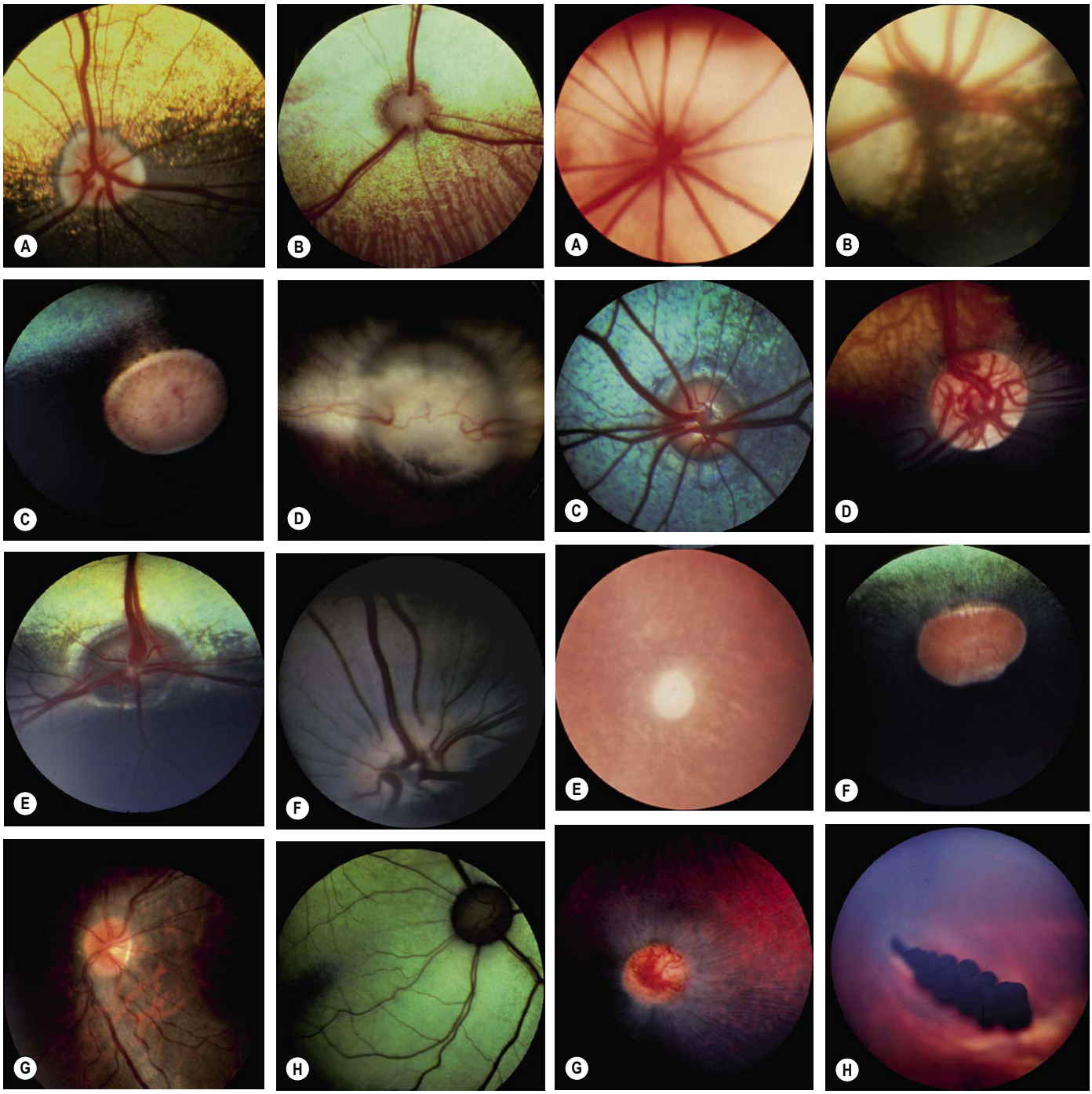


Figure 11.2 (i) The normal fundus, species comparison. (A) Family *Canidae* – English Setter (B) Family *Felidae* – Siamese (C) Family *Equidae* – Thoroughbred (D) Order *Lagomorpha* – Lop Eared Rabbit (E) Subfamily *Bovinae* – Guernsey (F) Family *Suidae* – Vietnamese Potbelly Pig (G) Order primates – Lowland Gorilla (H) Family *Felidae* – White Tiger. (ii) The normal fundus, species comparison. (A) Order *Rodentia*, Family *Muridae* – Rat (B) Family *Didelphidae* – Opossum (C) Subfamily *Caprinae* – Anglo-Nubian Goat (D) Family *Camelidae* – Alpaca (E) Order *Rodentia*, Family *Caviidae* – Guinea Pig (F) Family *Equidae* – Zebra (G) Family *Macropodidae* – Wallaby (H) Class *Aves* – Great Horned Owl.

Comparative Comments (continued)

pathologic usage, the term 'macula' refers to that portion of the retina having more than a single layer of ganglion cells. At the center of the macula are the fovea and the foveola, which are distinctive features of the primate retina within the Mammalia, but are present in birds and reptiles

- As noted, the pattern of retinal blood vessels is highly variable among different mammalian species. In the human retina, the intrinsic retinal blood vessels nourish the nerve fiber layer, ganglion cell layer, inner plexiform layer, and inner two-thirds of the inner nuclear layer. The choroidal vasculature in turn provides the blood supply to the outer one third of the inner nuclear layer, outer plexiform layer, outer nuclear layer, photoreceptors, and retinal pigment epithelium (RPE). Consequently, ischemia produced by intrinsic retinal vascular lesions produces atrophy of the inner retina, whereas choroidal ischemia produces outer retinal atrophy.

Significance of retinal disease to a mail-in pathology service

Primary retinal diseases, primarily congenital or hereditary retinal diseases, although fairly common, are seldom submitted for evaluation by a pathology service and, for that reason, are under-represented in the COPLOW collection.

- When the eyes of animals with retinal disease are submitted to an ocular pathologist, it is often not until there are secondary complications such as retinal detachment, cataract or intraocular hemorrhage that may subsequently lead to painful ocular disease, by which time the background retinal disease is chronic or otherwise changed by superimposed pathology
- When globes are submitted for evaluation of a disease primarily affecting the retina the likely reasons include the following:
  - A request for an opinion regarding a diagnosis of hereditary progressive retinal atrophy in an animal dying of other causes
  - A request to evaluate the retina for suspected toxic retinopathy in an animal dying of other causes
  - A request for an opinion from a researcher to describe the pathology in an animal with a novel funduscopic appearance.
  - The challenge is to be able to recognize the features of retinal disease that are due primarily to congenital or hereditary dysplasia and to differentiate these from secondary or superimposed abnormalities, related to retinal detachment or degeneration, glaucoma, trauma, or inflammation, for example
- Acquired retinal folds may be recognized in areas of retinal re-attachment subsequent to detachment, for example associated with sub-retinal effusion or exudates
- Before interpreting pathologic lesions as representative of an underlying breed-related retinal condition, there should be evidence in the form of tissue changes or cellular changes allowing the observer to distinguish a pathologic fold from a purely artifactual wrinkling of the retina. These might include gliosis, vascular changes, or changes in the density of intact retinal elements, such as photoreceptors or Müller cells.

CONGENITAL AND HEREDITARY DISEASES

Congenital disorders of the retina (see also Ch. 3)

Retinal folds and retinal dysplasia (Figs 11.3–11.6)

- Retinal dysplasia represents the disorganized development of retinal tissue. Lesions may be focal or multifocal curvilinear retinal folds; larger geographic lesions that may be accompanied by localized retinal degeneration and pigmentary changes, or, in its most severe form, total retinal non-attachment with vitreoretinal dysplasia
- There is seldom a clinical indication for enucleation of eyes with retinal folds or dysplasia in isolation. Often, eyes are removed for secondary or other unrelated disease and, after a significant amount of time has elapsed

Collie eye anomaly

- This recessively inherited abnormality of the canine fundus has its primary, ophthalmoscopically visible, effects on the RPE and choroid, with affected dogs demonstrating variable degrees of choroidal hypoplasia. A proportion of affected dogs also have colobomatous defects involving the optic nerve head, or peripapillary choroid and sclera
- Retinal detachment is not uncommon in severely affected eyes, and often relates to the presence of large colobomas, through which liquefied vitreous gains access to the subretinal space (see also Chs 3 and 12)
- The underlying genetic mutation, a deletion in the NHEJ1 has been identified and segregates with disease in all affected breeds, and a commercially available, mutation-based genetic test is available.

Congenital stationary night blindness in horses

- There is a breed-predisposition for the Appaloosa, in which the disease appears to be linked to the Leopard complex coat pattern
- Although pronounced behavioral and electrophysiological abnormalities are apparent, no ophthalmoscopic or histopathological abnormalities are detectable in affected animals.

Comparative Comments

- The most serious congenital disease of the retina is retinopathy of prematurity (ROP)
  - This disease can be induced in neonatal animals and animal models have been the source of extensive study of this abnormality, but ROP rarely occurs spontaneously in non-human species. However, a condition described previously in cats (see Ch. 3) shares many of the pathologic features of the human disease
  - ROP is classically defined as an oxygen-induced vitreoretinal disease of premature infants. ROP occurs bilaterally, almost exclusively in infants with an immature, incomplete retinal vascular system and particularly in premature infants who weigh less that 1.5 kg at birth and who receive oxygen therapy
  - The classic theories for pathogenesis were based on kitten, mouse, and puppy models, in which it was found that hyperoxia induces a vaso-obliterative phase with functional

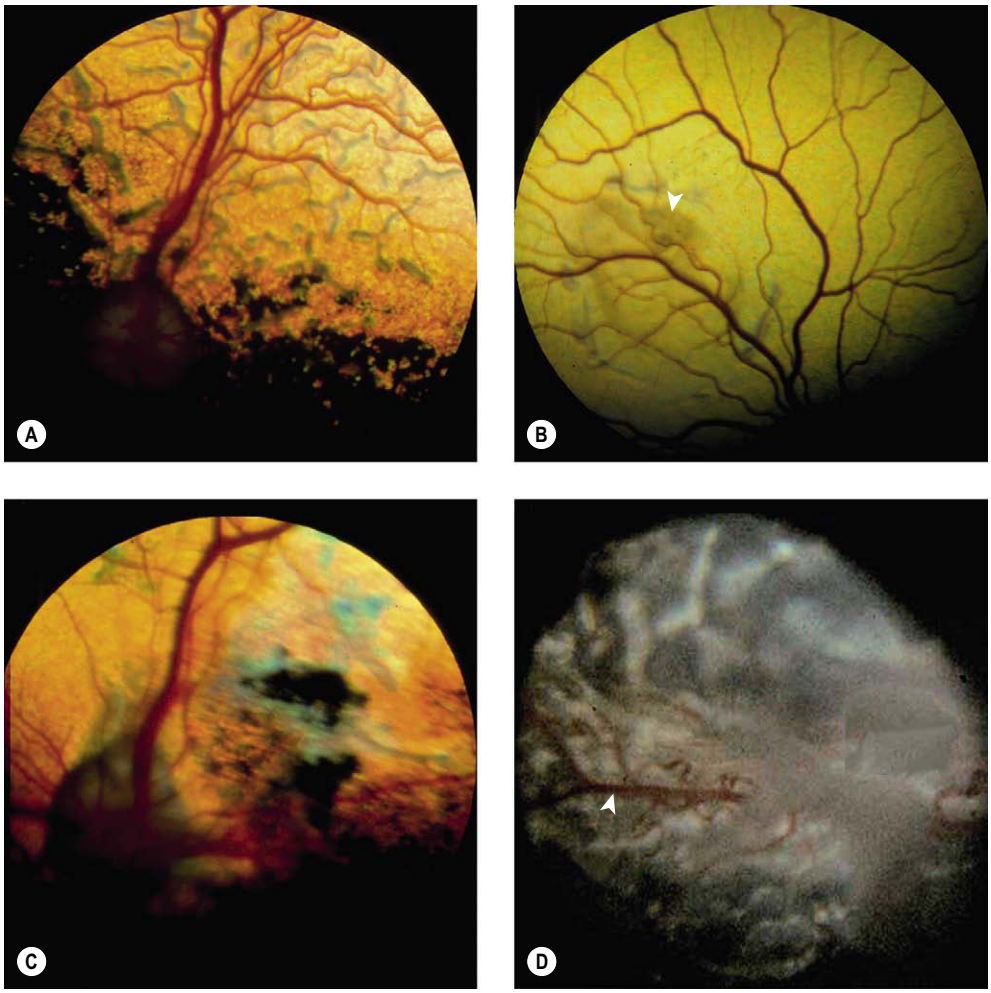


Figure 11.3 Canine retinal dysplasia, fundus. (A) Cocker Spaniel, 2 years old: the multiple retinal folds are best seen in the tapetal retina. (B) Golden Retriever, 2 years old: a single geographic area of dysplasia (arrow) was present in both tapetal retinas. (C) Springer Spaniel, 18 months old: the entire tapetal retina is disorganized with abnormal pigmentation, tapetal discoloration and areas of tapetal hyperreflectivity. (D) Labrador Retriever, 13 weeks old: the retina is totally detached. The gray lines represent retinal folds. A retinal vessel is seen at the arrow.

Comparative Comments (continued)

constriction of the immature retinal blood vessels, followed by structural obliteration. If the hyperoxia is sufficiently prolonged, on cessation of oxygen exposure the peripheral retina remains ischemic. A proliferative phase ensues, with intense fibrovascular proliferation beginning at the junction of the vascular and avascular zones and continuing through the internal limiting membrane into the vitreous

- Other important congenital abnormalities of the retina in humans include albinism, medullated nerve fibers, vascular anomalies, and congenital hypertrophy of the RPE.

Inherited retinal degenerations

Generalized progressive retinal atrophy (Figs 11.7–11.9)

- The collective term, progressive retinal atrophy (PRA) represents a diverse group of inherited, or presumed inherited, photoreceptor disorders that share a number of key features:
  - Bilateral, symmetrical ocular involvement
  - Photoreceptor degeneration that is progressive and leads to blindness
  - Common clinical features include:
    - Reduced pupillary light reflexes
    - Diffuse hyper-reflectivity of the tapetum, where present
    - Attenuation of the retinal blood vessels
    - Pigment clumping visible in the non-tapetal fundus
- Many of these disorders, particularly in dogs and cats, are considered to represent important models for human inherited retinopathies, and as such have been extensively characterized. Diagnostic pathologists are unlikely to be involved in these studies, but may be asked to voice an opinion regarding the presence or absence of PRA in a globe removed from a domestic pet, often years after onset of blindness. Such globes are typically enucleated because of a secondary or unrelated condition, e.g. glaucoma or ocular neoplasia
- Dogs are much more commonly affected by PRA than other species, as breeding practices have increased the incidence of inherited disorders in this domestic species. Most, but not all, forms of PRA are recessively inherited. X-linked PRA and autosomal dominant PRA have also been identified
- The disease features presented in this chapter clearly represent a simplistic generalization. Comprehensive discussion of the full extent of current knowledge of the incidence, early structural and functional abnormalities and the genetic basis of this spectrum of retinal disorders is outwith the scope of this text. Hence, a general synopsis is provided for pathologists attempting to interpret ocular specimens submitted for

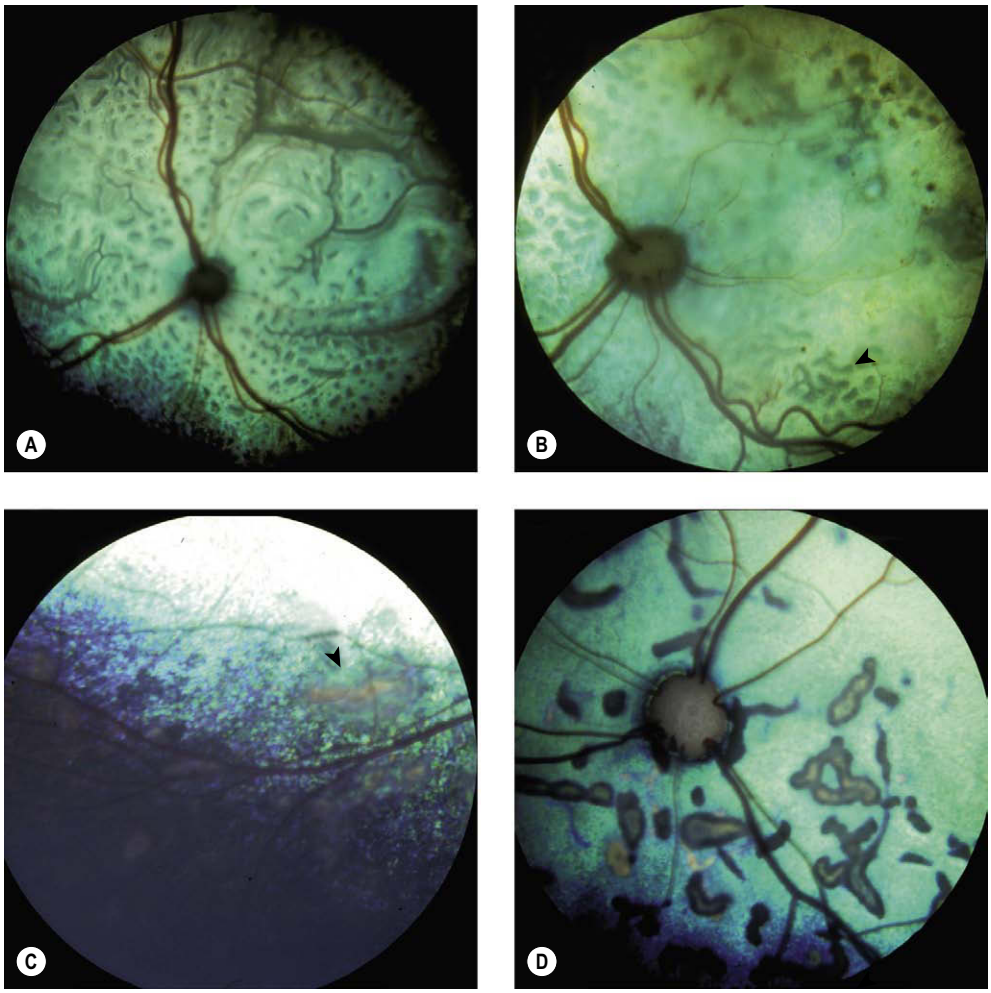


Figure 11.4 Feline retinal folds, congenital and acquired, fundus. (A) DSH, 6 months old: the many folds are commonly found in conjunction with congenital cataracts. (B) DSH, 9 years old: the elevated systolic blood pressure resulted in a peripapillary retinal detachment and numerous retinal folds (arrow). (C) DSH, 6.5 years old: the linear and focal pink lesions are best seen near the tapetal junction (arrow). The etiology in this blind cat was *Enterococcus avium*, identified in the cerebrospinal fluid. (D) DSH, 9 months old: the multiple linear pink lesions appear to be in the outer layers of the retina. Lymphosarcoma was diagnosed on histopathology.

diagnostic purposes and for the clinicians who will be making use of those interpretations

- This diverse group of disorders may be broadly subdivided into:
  - Early onset: photoreceptor dysplasias and dystrophies
    - Morphological and electrophysiological abnormalities are detectable prior to maturation of the retina (i.e. prior to about 8 weeks in dogs) and significant visual deficits are evident early in life
  - Late onset: photoreceptor degenerations
    - Although the photoreceptors appear morphologically normal in young animals, rod photoreceptor outer segments are often preferentially affected, becoming shortened, disorganized, then degenerating. Ultimately, cone photoreceptors are also affected. Blindness ensues in middle-aged adults
  - These disorders may be further classified according to the principal photoreceptor type involved
    - Many of the well-characterized forms of PRA affect the rod photoreceptors initially and more severely
    - Cone dystrophies and degenerations are much less common than disorders involving the rod photoreceptors, and many forms do not cause night blindness, or do not demonstrate rod photoreceptor abnormalities until late in the course of disease
- Early morphologic features of PRA include:
  - Shortening, disorganization and distortion of photoreceptor outer segments, progressing to loss of photoreceptor outer and inner segments. The age of onset and relative extent of involvement of rods and cones depends on the underlying disease process
  - Loss of photoreceptor nuclei, with thinning of the outer nuclear layer
  - Although retinal disease is diffuse, often photoreceptor loss is not uniform across the fundus. This topographic and temporal gradation of lesion severity differs between the various disorders
- Morphologic features of longstanding PRA, in globes removed for other reasons, include:
  - Retinal atrophy, most profoundly affecting the outer retina
  - Presence of phagocytic cells within the neurosensory retina
  - Photoreceptor atrophy progresses to end-stage retinal atrophy with gliosis
  - Common intraocular complications of long-standing PRA in dogs include:
    - Retinal detachment
    - Cataract, which may, in turn, lead to lens-induced uveitis or lens luxation, and to glaucoma

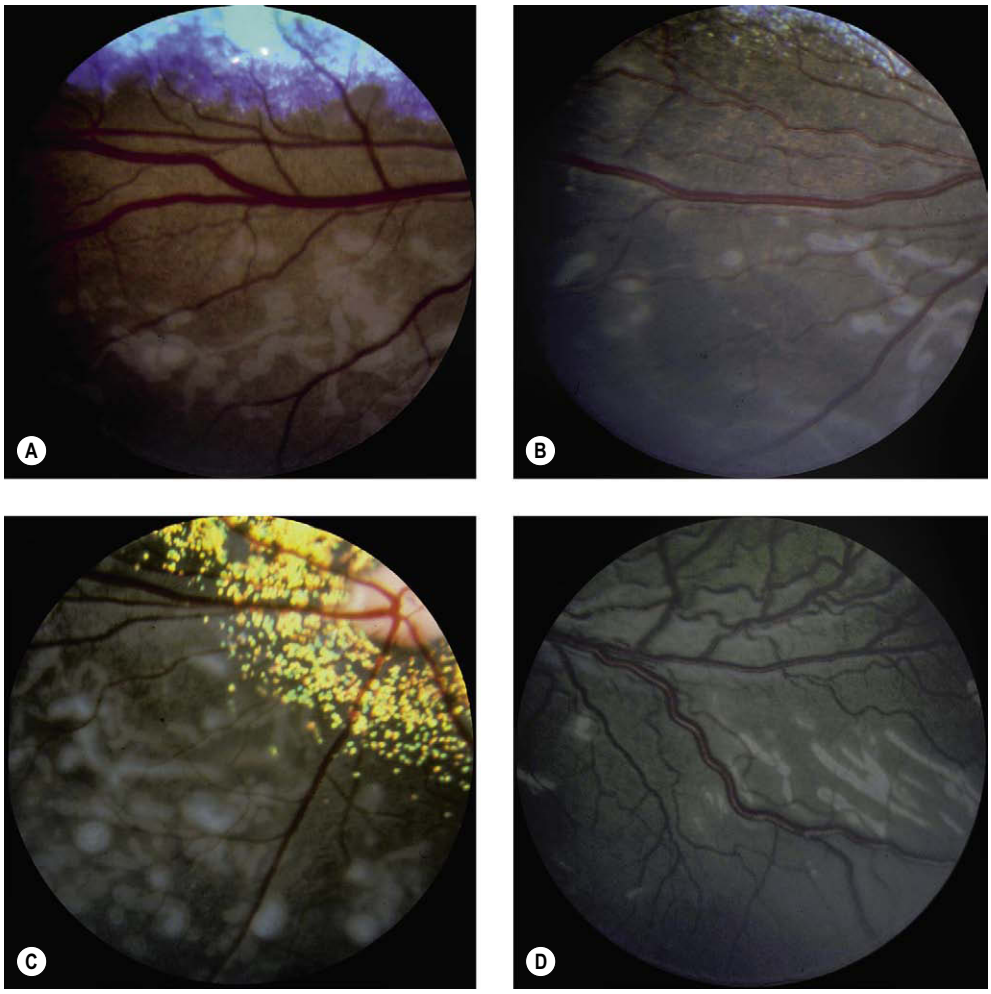


Figure 11.5 Acquired retinal folds, canine. (A) German Short-haired Pointer, 7 months old: the multiple retinal folds in the non-tapetal retina were associated with *Coccidioides*, based on serology. (B) German Shepherd Dog, 2.5 years old: the linear retinal folds were caused by systemic *Cryptococcus*, based on histopathology. (C) Beagle, 5 years old: the multiple folds and focal edema in this blind eye were caused by ivermectin toxicity. (D) French Bulldog, 1 year old: retinal folds found in both eyes from this blind dog were presumed to be immune mediated.

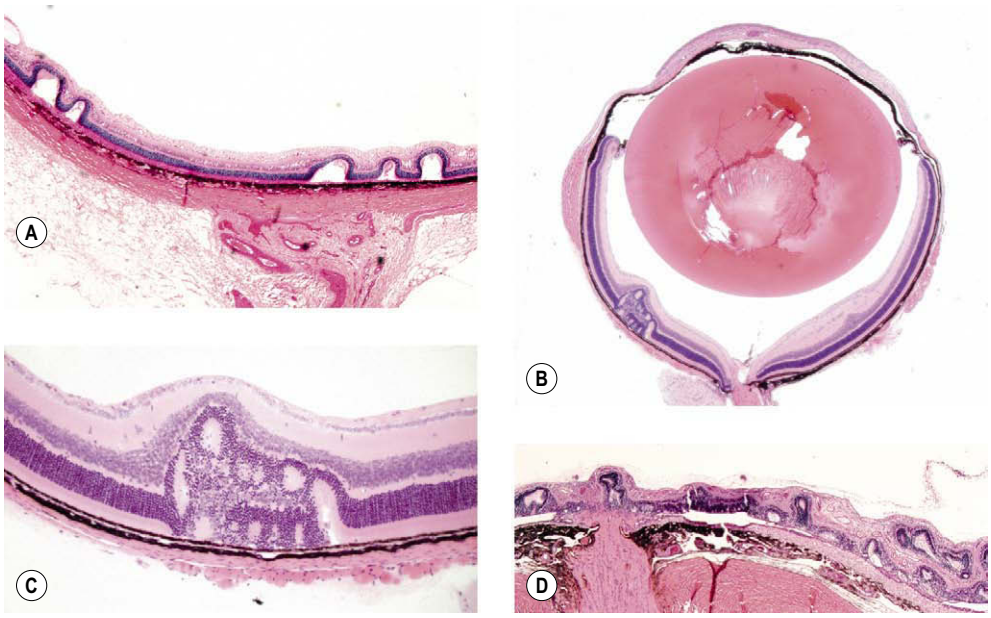


Figure 11.6 Retinal folds and retinal dysplasia, pathology. (A) Low magnification photomicrograph of a canine retina with retinal folds. (B,C) Subgross and higher magnification photomicrographs showing retinal dysplasia. (D) Low magnification photomicrograph of a dog retina showing widespread retinal dysplasia.

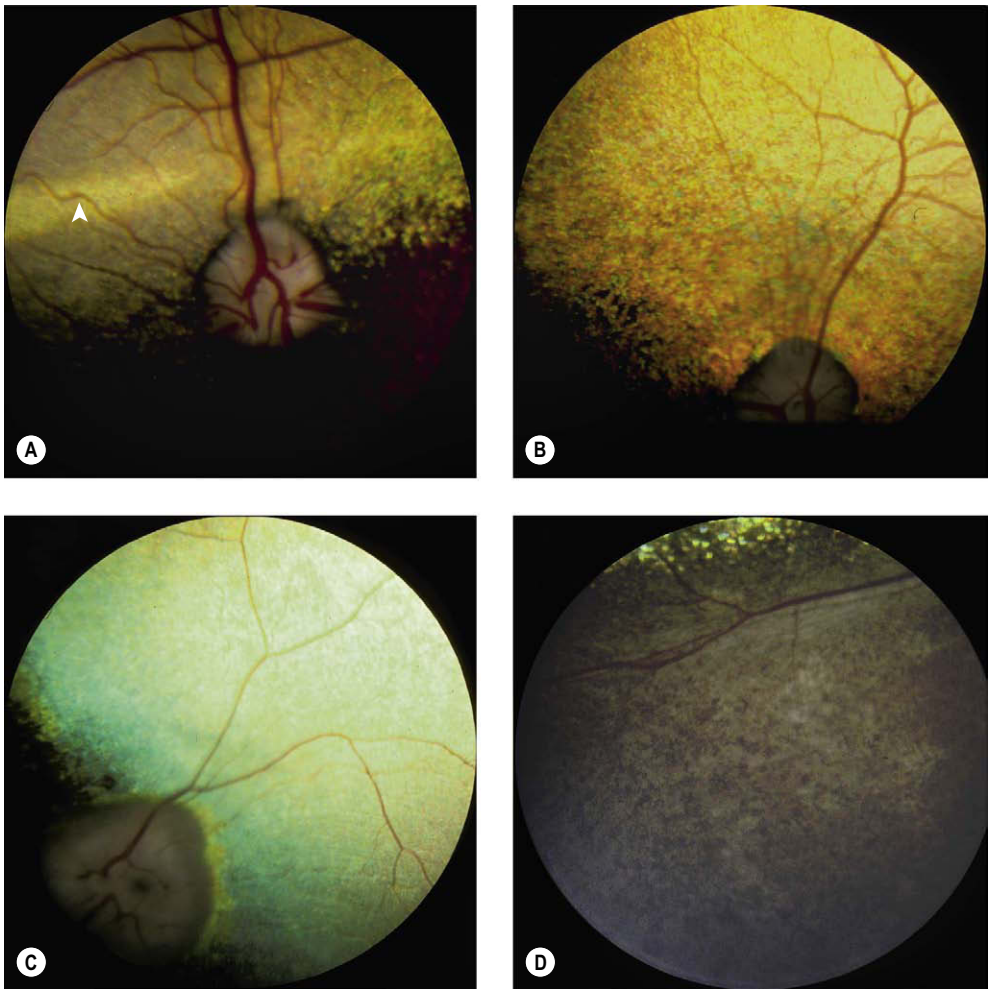


Figure 11.7 Canine progressive retinal atrophy, fundus. (A) English Cocker Spaniel, 4 years old: the horizontal band (arrow) superior to the optic disc was an early lesion of progressive retinal atrophy (PRA), confirmed by an electroretinogram. (B) Poodle, 4 years old: a neutral density filter was used to reduce glare from the tapetal hyperreflectivity. Retinal vessels are also attenuated. (C) Labrador Retriever, 5 years old: the tapetum is hyperreflective, and all retinal vessels are severely attenuated. (D) Australian Shepherd, 6 years old: the cobblestone appearance in the non-tapetal retina is due to clumping of pigment and depigmentation.

- It is seldom possible to definitively diagnose PRA on the basis of morphological findings alone. It is generally only possible to say that the changes seen are consistent with that diagnosis
  - Knowledge of commonly affected breeds may raise an index of suspicion for inherited PRA
  - Very commonly affected breeds include the miniature and toy Poodle, Labrador retriever, American and English Cocker spaniel (prcd) and Miniature Schnauzer, although primary photoreceptor dystrophies and degenerations have been reported and characterized, or are suspected to be inherited, in a large number of breeds. The reader is referred to the most recent edition of *Ocular Disorders Presumed to be Inherited in Dogs*, published by ACVO for regularly updated information on affected breeds
- Differential diagnoses for retinal degeneration include:
  - Sudden acquired retinal degeneration syndrome (SARDS) in dogs
  - Toxic retinopathies
  - Choroidal perfusion problems/vascular disease
  - Nutritional retinopathies
  - Diseases of the RPE such as lipofuscinosis
- A number of genetic mutations have been identified in affected breeds and genetic tests are available for an ever increasing number of different forms of PRA. The reader is referred to online molecular genetic and citation databases, such as OMIM, OMIA and Medline, as well as other online resources such as the website of the commercial genetic testing company, Optigen (www.optigen.com) for up-to-date information on available tests
- Inherited photoreceptor degeneration in cats:
  - Aside from retinal degeneration secondary to vascular disease, nutritional or toxic causes (discussed later in this chapter), diffuse photoreceptor degeneration is uncommon in cats
  - Clinical and pathologic features of inherited retinal degeneration are broadly similar to canine PRA, as described in the previous section
  - Two distinct forms of inherited retinal degeneration have been extensively studied in the Abyssinian cat:
    - An early-onset form with dominant inheritance
    - A later-onset, more slowly progressive form with recessive inheritance
  - An early-onset, recessively inherited retinal degeneration has also been described in a colony of Persian cats
  - Older Siamese cats have also been over-represented in some studies of feline retinal degeneration.

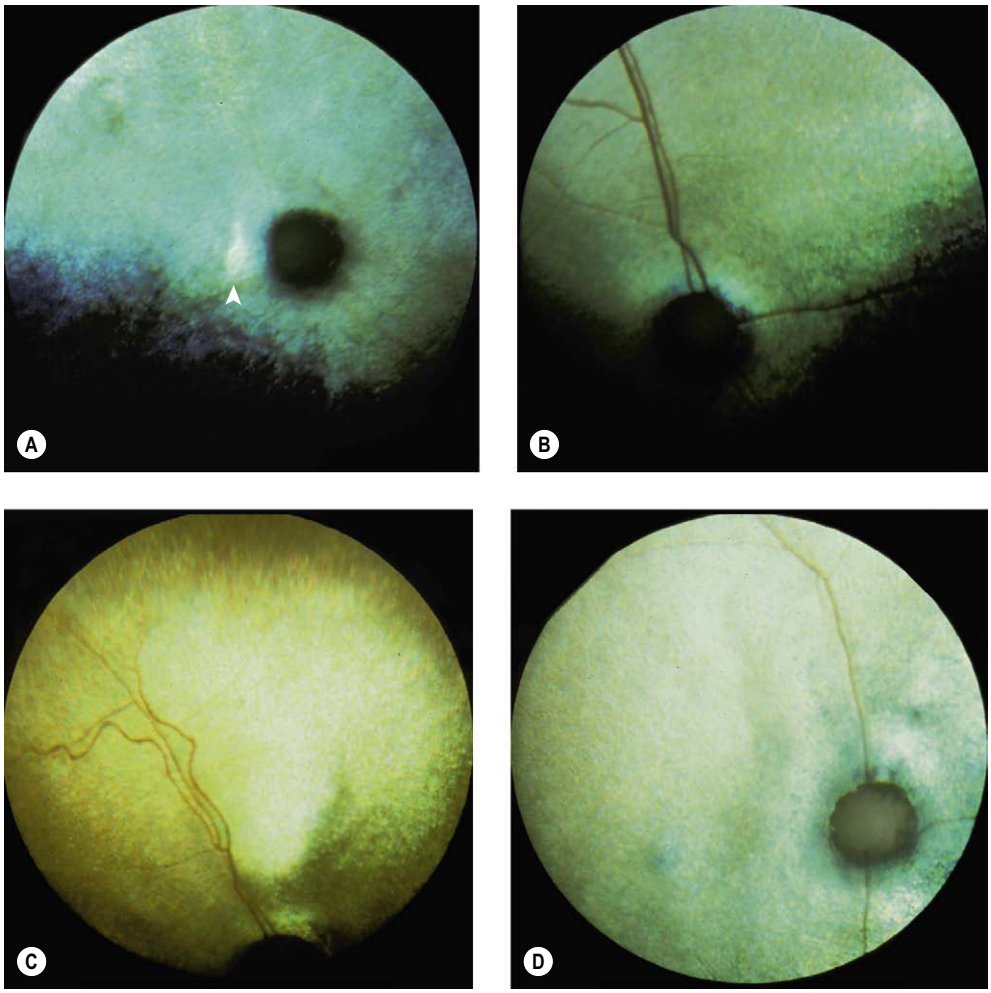


Figure 11.8 Feline retinal atrophy, fundus. (A) Abyssinian, 7 months old: a neutral density filter was used to reduce glare from the tapetal hyperreflectivity and accounts for the dark optic disc. The retinal vessels (arrow) are severely attenuated. (B) Abyssinian, 6 years old: the tapetum is hyperreflective and the retinal vessels are attenuated. (C) Siamese, 14 years old: the tapetum is severely hyperreflective and the retinal vessels are extremely attenuated. (D) Burmese, 3 years old: the optic disc is pale, the retinal vessels are severely attenuated, and the tapetum is hyperreflective.

Retinal dystrophy in Briard dogs, congenital stationary night blindness (CSNB), lipid retinopathy

- Clinical features of this disease include:
  - Affected dogs are night-blind, with variable degrees of visual impairment in daylight conditions
  - Fundus appearance is normal for the first few years of life but slowly progressive, subtle color changes may be noted in the tapetal fundus, with white, yellowish or brown spots visible in some animals and associated with tapetal hyper-reflectivity
- Morphological features of this disease include:
  - Vacuolation of the RPE, with accumulation of large, lipid-like, electron-lucent inclusions
  - Disorganization and degeneration of rod outer segments
- This disease is caused by a mutation in the gene which codes for RPE65, an RPE protein which is essential to the regeneration of visual pigment that, in turn, is vital to photoreceptor function
- This disease is not common but is considered an extremely important animal model for a human disease (Leber congenital amaurosis) that can result from the same genetic mutation
  - Reports of restoration of vision in affected dogs marked the first successful demonstration, in a species with comparable eye size to that of humans, of gene therapy to preserve or restore vision in a primary, inherited retinal disease.

Canine multifocal retinopathy (Fig. 11.10)

- This unusual retinopathy is characterized by multifocal gray or tan lesions that appear throughout the fundus of young dogs
- Morphologically, these lesions correspond with serous detachments of the retina and RPE, and associated multi-focal areas of RPE hypertrophy, lipofuscin accumulation (see below) and degeneration. These RPE lesions are accompanied by variable degrees of neurosensory retinal degeneration
- Canine multifocal retinopathy demonstrates autosomal recessive inheritance in the breeds characterized to date
- Mutations in the bestrophin gene, which codes for a protein that is expressed in the RPE, have been identified in the Great Pyrenees, English Mastiff and Bull Mastiff (*cmr1*) and Coton du Tulear (*cmr2*) and in humans with Best macular dystrophy.

Lysosomal storage disorders and the neuronal ceroid lipofuscinoses

- This diverse group of neurodegenerative disorders are characterized by progressive neurological abnormalities and gradual loss of vision. Storage products accumulate within lysosomes in various tissues throughout the body, impairing tissue function

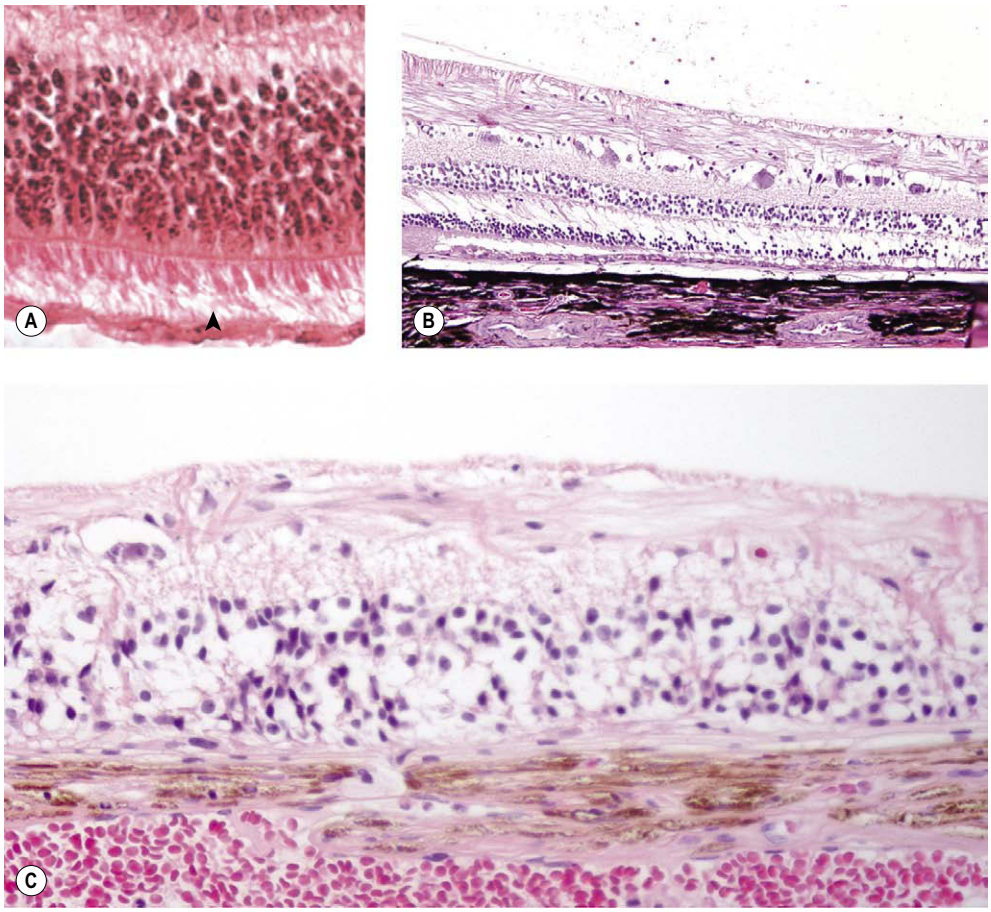


Figure 11.9 Canine progressive retinal atrophy, pathology. (A) Photomicrograph of the early stages of progressive retinal atrophy (PRA) in an Irish Setter puppy showing early atrophy and degeneration of photoreceptor outer segments (arrow). The only appreciable change is increased space between the outer segments. (B) Photomicrograph of a canine retina from a Poodle whose eye was removed because of an iridociliary adenoma. This dog had vision loss and had a fundic exam which showed retinal atrophy typical of PRA. (C) Photomicrograph showing end-stage outer retinal atrophy from a dog with long-standing disease. Histopathology on client animals with eyes removed for other reasons is not a very reliable method for making a definitive diagnosis of PRA, and it is not at all useful in distinguishing the many forms of PRA from one another.

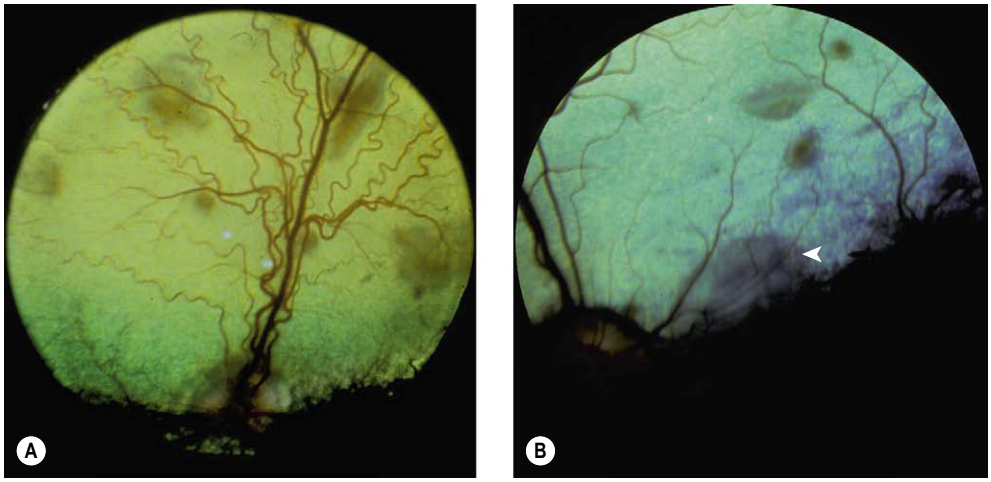


Figure 11.10 Canine multifocal retinopathy (A) Great Pyrenees, 1 year old: multiple tan lesions are present deep to the retinal vessels. Serous retinal detachments are associated with several lesions. (B) English Bulldog, 2 years old: multiple lesions are present in the tapetal fundus. The lesion at the tapetal junction has a serous separation of retinal layers at the arrow.

- Several of these disorders have been extensively characterized in domestic species, including sheep, dogs and cats, and serve as valuable animal models for human diseases
- The range of lysosomal storage disorders that may be associated with retinal pathology includes, but is not limited to:
  - GM1 gangliosidosis
  - MPS VII
  - Fucosidosis
- The neuronal ceroid lipofuscinoses (NCL) are a heterogeneous group of diseases characterized by intracellular accumulation of ceroid lipofuscin (see below)
  - In contrast to disorders associated with photo-oxidation, in which lysosomal storage bodies primarily accumulate in the RPE, in NCL this autofluorescent ceroid lipopigment generally accumulates within the neurosensory retina, particularly retinal ganglion cells, as well as other tissues

- Characteristic 'fingerprint profiles' may be seen within these granules on ultrastructural studies.

Comparative Comments

A number of generalized chorioretinal degenerations are seen in humans, many of which have striking similarities to those occurring in dogs and other species. Although clinically and histologically there is little evidence of inflammation, this family of diseases is referred to as retinitis pigmentosa and has a complex and varied genetic basis. Although eyes with these conditions are rarely submitted to the pathology laboratory, the disease is characterized primarily by the loss of rod photoreceptor cells by apoptosis, with cone photoreceptors generally degenerating secondarily to the rods.

OTHER DEGENERATIVE CONDITIONS OF THE RETINA

Sudden acquired retinal degeneration syndrome (SARDS) in dogs

Although SARDS is a relatively common cause of sudden-onset blindness, there is little indication, beyond research interest, to remove the eyes from SARD-affected animals for pathologic evaluation.

- Typically, globes from dogs with SARDS are only submitted to a pathologist after the animal dies for other reasons, or if they subsequently develop complicating ocular conditions that necessitate enucleation, or if they adjust so poorly to their loss of vision that euthanasia is elected
- There are only 20 cases in the COPLOW collection.

Clinical features typical of SARDS in dogs

- Sudden onset of blindness noticed by the owner
- Dilated resting pupil size, with pupillary light reflexes that can still be elicited in response to intense stimuli that are a source of blue light
- Normal, or near normal, fundus appearance in early disease
- A 'flat' electroretinogram, indicating absence of photoreceptor function/phototransduction.
- Over many months, ophthalmoscopic findings are consistent with gradually progressive diffuse retinal degeneration
- The clinical history may suggest ill-defined metabolic problems including:
  - Polyuria and polydipsia
  - A high-normal ACTH response test or abnormalities in the results of other tests of adrenal cortical function
  - Obesity, or recent weight gain.

Morphological features of the retina in SARDS (Fig. 11.11)

- Early in the course of disease, the retina is nearly normal except a narrowing of the outer plexiform layer
- Apoptotic photoreceptor cells may be detected within the outer nuclear layer
- From several weeks or months into the course of disease, there is an atrophy of photoreceptors, resembling PRA. However, unlike early stages of PRA, involvement is diffuse and relatively uniform throughout the retina
- Lymphoplasmacytic inflammatory cells are seen but are present in very small numbers
- The retinal degeneration is slowly progressive and ultimately, can involve all the layers of the retina.

Feline central retinal degeneration, taurine deficiency (Figs 11.12, 11.13)

- Taurine deficiency in cats is associated with both retinal disease and dilated cardiomyopathy
- Cats need a dietary source of taurine as they are unable to synthesize adequate amounts of this amino acid from cysteine
- The classical retinal disease is a focal outer retinal degeneration, initially seen in the area centralis and slowly progressing to involve both the temporal and nasal fundus superior to the optic nerve head
- In the earliest stages of this disease, cone disorganization and dysfunction is greater than involvement of rod photoreceptors
- In chronically deficient cats, more generalized photoreceptor degeneration is seen and these cats may be irreversibly blind (Fig. 11.13)
- Taurine deficiency should be considered in the differential diagnosis of photoreceptor degeneration in cats.

Lipofuscin in the RPE and effects on the retina (Fig. 11.14)

Lipofuscin is a general term for a variety of autofluorescent compounds containing cross-linked proteins and lipids. The precise constituents of lipofuscin vary according to the tissue in which it is formed as a lysosomal storage product.

- The main constituent fluorophore of RPE lipofuscin has been identified as A2E, a product of vitamin A metabolism and photoreceptor membrane lipids.
- Accumulation of small amounts of lipofuscin in the RPE is a common finding in eyes submitted to COPLOW
- Lipofuscin may be recognized as a feature of normal aging, and is also known as 'age pigment'
- Lipofuscin in the RPE is probably the most common ocular abnormality seen in exotic or wild species in the COPLOW collection
- Lipofuscin accumulates in conditions associated with enhanced oxidative stress, or a reduction in the activity of intrinsic defense mechanisms against oxidative stress.
- Too much lipofuscin in the RPE impedes further phagolysosomal degradation, contributes to photo-oxidative damage and can impact photoreceptor function, leading to outer retinal degeneration.

Clinical features of retinal diseases associated with increased lipofuscin in the RPE cells

- Accumulations of RPE lipofuscin may be visible within the tapetal fundus (where the RPE is normally non-pigmented) as multiple foci and patches of light-brown pigment
- Subsequent retinal degeneration may lead to other changes such as attenuation of retinal blood vessels, pigmentary changes in the non-tapetal fundus, and focal regions of tapetal hyper-reflectivity
- Depending on the underlying cause of lipofuscin accumulation, other systemic signs of disease such as neurologic abnormalities or muscle weakness may be evident.

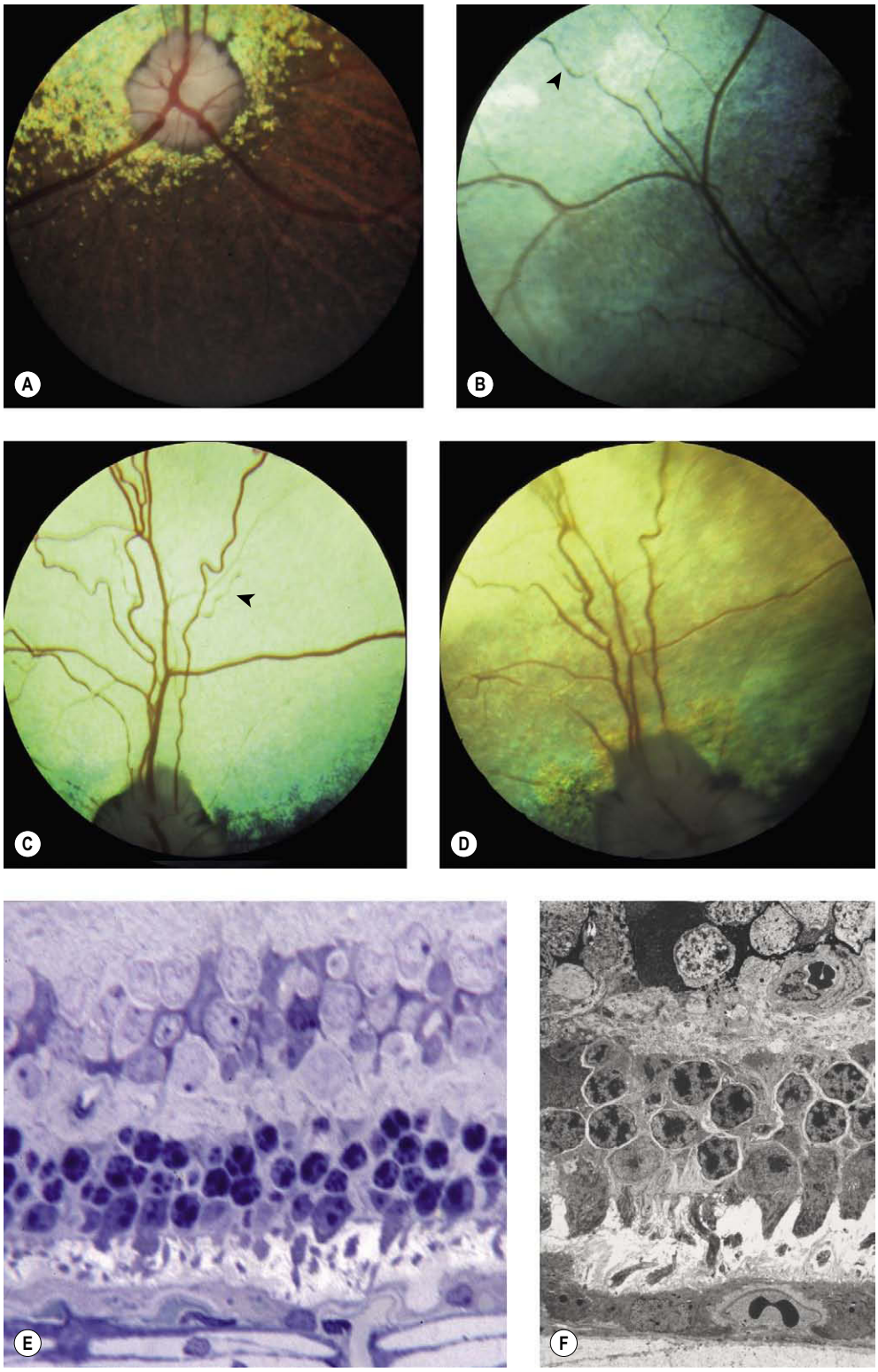


Figure 11.11 Canine sudden acquired retinal degeneration syndrome (SARDS). (A) Mixed Breed, 8 years old: the optic disc and non-tapetal retinal appear ophthalmoscopically normal. (B) Miniature Schnauzer, 9 years old: the tapetal retina has a diffuse hyperreflectivity, and the vessels are attenuated with areas of sacculation (arrow). (C) Basset Hound, 7 years old: the retinal vessels are attenuated and sacculated (arrow). (D) Basset Hound, 11 years old: this is the same eye as in C, 4 years later. Tapetal hyperreflectivity has increased and the retinal vessels, although still visible, are subjectively more attenuated. (E,F) Plastic section photomicrograph (E, Toluidine blue stain) and low magnification electron micrograph (F) of a SARDS-affected dog retina showing photoreceptor atrophy.

Morphologic features of retinal diseases associated with increased lipofuscin in the RPE cells

- Lipofuscin appears as light brown granules in the cytoplasm of the RPE cell, that stain positively with PAS
- Lipofuscin granules demonstrate characteristic yellow autofluorescence when non-stained sections are observed under illumination with blue light
- On transmission electron-microscopy, lamellar membrane profiles are often observed within these lysosomal storage bodies
- Pathologic accumulation of lipofuscin in the RPE is a significant finding that can contribute to vision loss
  - RPE cells are responsible for the continuous phagocytosis and lysosomal degradation of proteins and

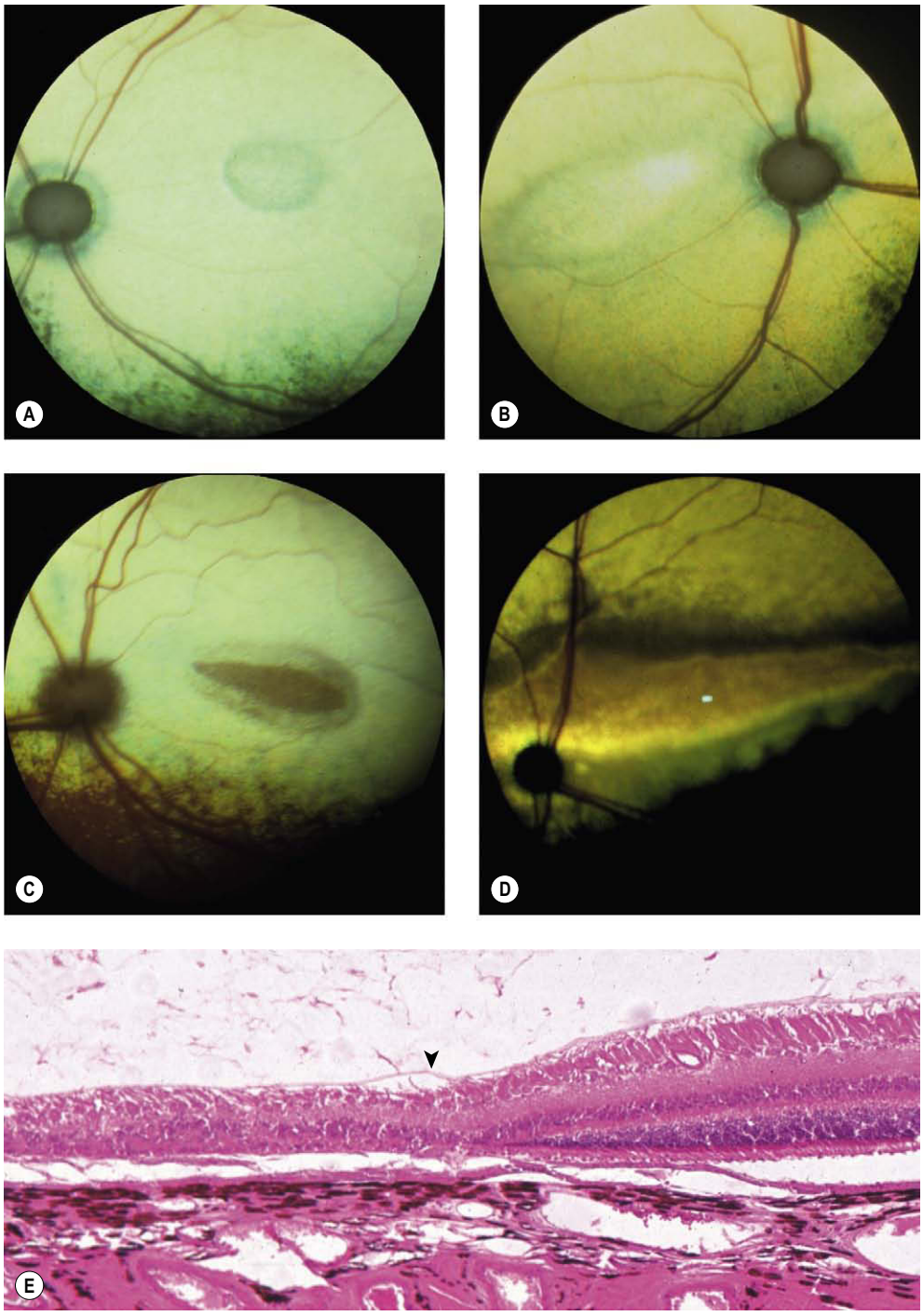


Figure 11.12 Feline central progressive retinal atrophy, FCRD. (A) DSH, 8 years old: the small elliptical area of hyperreflectivity is located temporally in the area centralis. (B) DSH, 8 years old: in this right eye, the center of the elliptical lesion is hyperreflective due to the angle of light striking the retina and reflecting to the viewer. (C) Siamese, 14 years old: in the left eye, the center of the lesion appears dark and the margin appears hyperreflective. (D) DSH, 11 years old: photographed through a neutral density filter and a 28-diopter lens, this hyperreflective lesion is superior to the disc and extends nasally and temporally. (E) Low magnification photomicrograph showing abrupt loss of the photoreceptors (arrow), while the inner retinal layers persist, typical of central retinal atrophy in cats.

phospholipids in photoreceptor outer segment membranes throughout life
- This membrane degradation occurs in an environment that is exposed to light, which can contribute to oxidative damage to the tissues and favors lipofuscin formation.

Large amounts of lipofuscin in RPE cells

Large amounts of lipofuscin in RPE cells might be an indication of any of the following problems:

- Absolute or relative deficiencies in vitamin E, or other antioxidants
  - Absolute or relative dietary deficiency or malabsorption of vitamin E has been associated with retinal degeneration in a wide range of species, including dogs and horses
- Central progressive retinal atrophy, retinal pigment epithelial dystrophy (RPED) (Fig. 11.15)
  - Although encountered in European populations of several dog breeds that include, most notably, the English Cocker Spaniel, Labrador and Briard, this is a rare condition in the United States

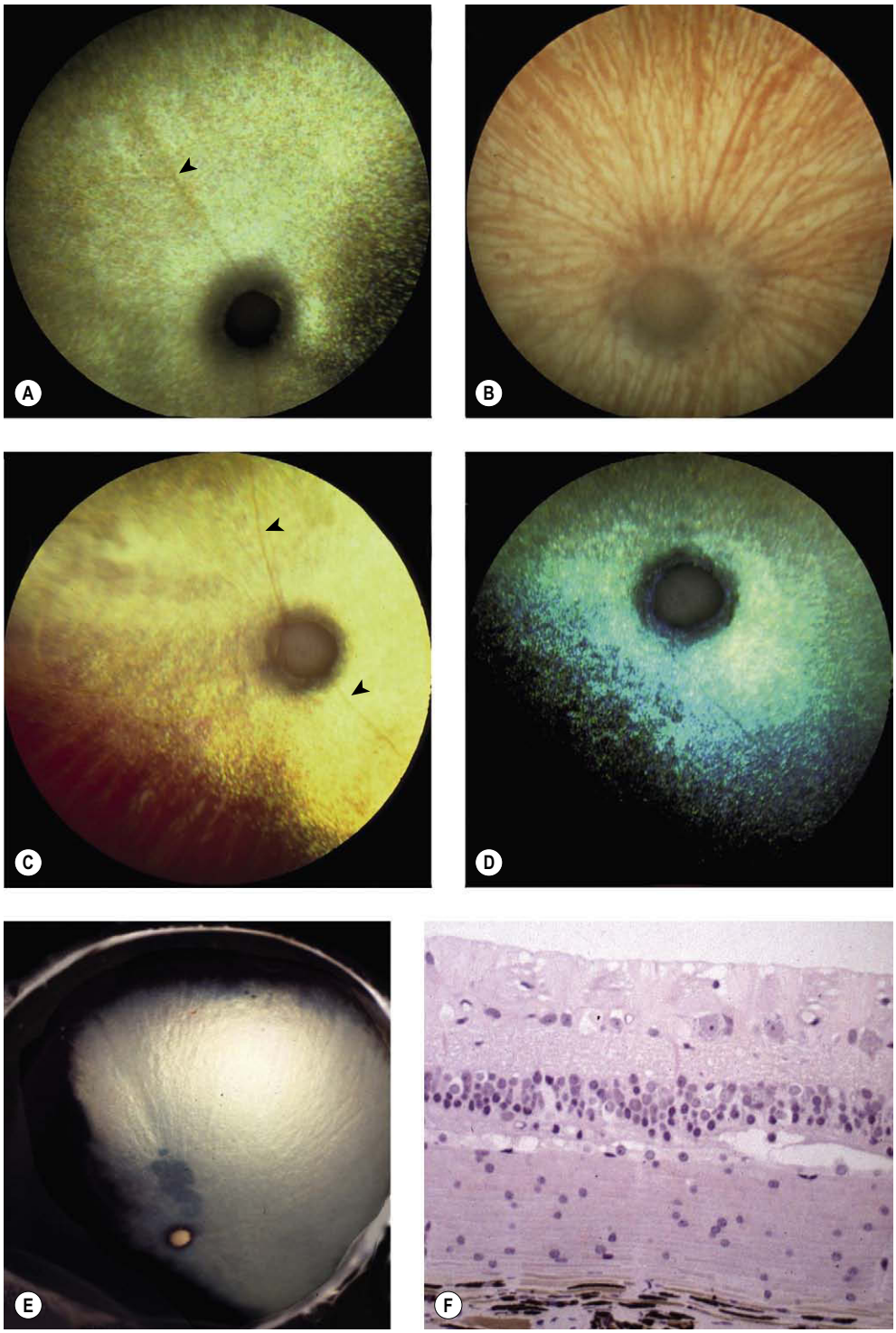


Figure 11.13 Feline generalized retinal atrophy. (A) Tonkinese, 3 years old: taken with a neutral density filter to reduce the tapetal hyperreflectivity, the optic disc appears very dark. Retinal vessels (arrow) are extremely attenuated. (B) DSH, 1 year old: the optic disc is pale. It is difficult to see any attenuated retinal vessels in this albinoid and atapetal fundus. (C) Himalayan-Persian, 4 years old: attenuated retinal vessels (arrows) are still visible in the hyperreflective tapetal retina. (D) DSH, 2 years old: the tapetum is hyperreflective and there are no discernible retinal vessels. (E) Gross photograph of an affected cat globe showing blood vessel atrophy. (F) Photomicrograph of the retina from an affected cat that was blind and died from other causes, showing photoreceptor atrophy.

- Clinical features of RPED include:
  - Brown or tan pigment foci that are visible throughout the tapetal fundus
  - Slowly progressive retinal degeneration, with multifocal areas of increased tapetal reflectivity and pigment clumping within the non-tapetal fundus
  - Progressive loss of vision
  - In some affected dogs, signs of ocular disease are accompanied by neurological abnormalities including ataxia, proprioceptive deficits and muscle weakness
- Morphologic features of RPED include:
  - Hypertrophy and degeneration of the RPE, with associated degenerative changes in the outer, neurosensory retina

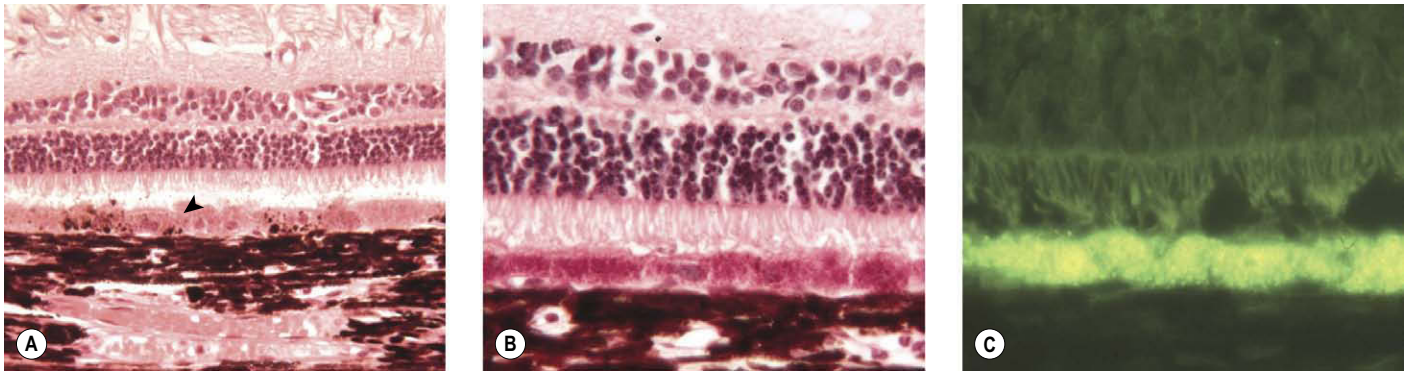


Figure 11.14 Retinal lipofuscinosis. (A) Photomicrograph of a dog retina showing swollen RPE cells with accumulated light brown pigment (arrow) and minimal photoreceptor outer segment disruption and atrophy. (B) Photomicrograph of the same retina as A, stained with PAS, showing the intense PAS-positive staining of lipofuscin. (C) Photomicrograph of the same retina with fluorescence microscopy. A non-stained section was illuminated with an ultraviolet light to excite the autofluorescent lipofuscin.

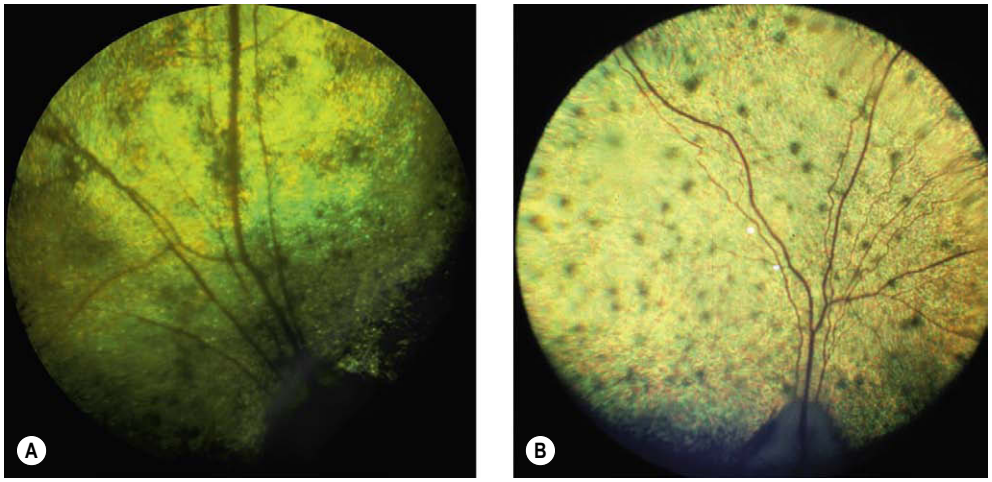


Figure 11.15 Canine central progressive retinal atrophy retinal pigment epithelial dystrophy (A) German Shepherd Dog, 12.5 years old; Bilateral focal areas of tapetal pigmentation were present. Mild attenuation of retinal vessels and tapetal hyperreflectivity are also present. (B) Brittany Spaniel, 2 years old: Multiple brown lesions are present in the tapetal fundus. The retinal vessels appear subjectively attenuated.

  - Widespread accumulation of lipofuscin granules within the RPE
  - Lesions are initially most severe at the posterior pole, spreading to involve the entire retina as the disease progresses
  - Other lesions that may be seen in tissues of affected dogs if submitted for necropsy include:
    - Lipofuscin accumulation in brainstem nuclei
    - Central neuro-axonal dystrophy and degeneration, that is most prominent in the sensory relay nuclei of the brainstem
    - Lipofuscin accumulation in smooth muscle, in particular intestinal lipofuscinosis
- These abnormalities are essentially identical to those associated with dietary vitamin E deficiency in dogs
- Low plasma alpha-tocopherol values have been reported in affected dogs fed diets containing adequate vitamin E. Thus, this familial disease probably represents an ocular manifestation of systemic antioxidant deficiency. The disease appears to be due to abnormal metabolism or transportation of vitamin E, rather than a primary retinal disorder

- Equine motor neuron disease is frequently accompanied by a characteristic retinopathy
  - Pigmented linear lesions are visible throughout the tapetal fundus, often forming a distinctive reticulated pattern
  - Accumulation of lipofuscin in the RPE is associated with retinal degeneration
  - Abnormal blood and tissue levels of vitamin E have been implicated in the development of retinal degeneration as well as neurodegenerative disease in horses
  - Signs of neurological dysfunction are usually the presenting complaint
- Canine multifocal retinopathy (see earlier in this chapter)
- Increased exposure to ultraviolet light and blue light
  - Continuous exposure to intense sunlight or high levels of artificial light may increase lipofuscin accumulation
  - Much of the short wavelength light to which the eye is exposed is filtered by the lens, hence exposure to this 'light hazard' is increased in aphakic animals
- Increased or altered turnover of photoreceptor outer segments
  - As may occur in association with photoreceptor degeneration

- Dietary exposure to factors which contribute to oxidative stress such as high concentrations of fats
- Accumulation of large amounts of lipofuscin in the retina can also result from specific intrinsic errors of metabolism, such as the neuronal canoid lipofusinoses (see earlier in one chapter and metabolic problems involving lipo formatting on breakdown)

Comparative Comments

- The deposition of lipofuscin in the RPE of non-human animal retinas is related to the entity of drusen seen in human eyes
- Drusen are localized deposits of extracellular material between the basement membrane of the RPE and the inner collagen layer of Bruch's membrane. They are classified clinically and pathologically into several subtypes: hard, soft, diffuse, basal, nodular, mixed, and calcified regressing drusen
- The appearance of drusen is the first clinically detectable feature of age-related macular degeneration. It is not clear, however, whether the photoreceptor atrophy occurring in age-related macular degeneration is a primary abnormality of the photoreceptors or is secondary to the drusen and other underlying changes in the RPE and Bruch's membrane.

Age-related degenerative changes

Peripheral cystoid degeneration (Fig. 11.16)

- The peripheral retina in older dogs is often distorted because of the formation of hyaluronic acid filled cysts at the junction between the peripheral retina and the pars plana of the ciliary body (the *ora ciliaris retinae*)
- This is an aging change that is very common and of no known clinical significance
- In cats, similar cysts are not located in the retina but in the pars plana epithelium of the ciliary body
- In horses, the cysts may be multiple, but are often solitary and arise at the pars plana.

Accumulation of lipofuscin

- In the RPE (see previous section).

Equine senile retinopathy (Fig. 11.17)

- The aged horse has a peripheral retinal degeneration characterized by multifocal, neurosensory retinal atrophy and degeneration with pigmentary changes
- The peripheral RPE appears to be colonized by pigmented and non-pigmented cells from the ciliary body epithelium
- Areas colonized by pigmented cells demonstrate local hyperpigmented foci and neurosensory retinal atrophy
- Areas colonized by non-pigmented cells have neurosensory retinal atrophy with deposition of basement membrane matrix material in the degenerate retina
- Since the degeneration is generally confined to the periphery, this condition seldom results in clinically apparent reduction of vision.

Comparative Comments

A counterpart to peripheral cystoid degeneration, described in dogs, is seen in humans and generally termed 'peripheral microcystoid degeneration.' These are aggregates of microcysts occurring just posterior to the ora serrata, presumably due to degenerative occlusive disease in the peripheral retinal arterioles.

Peripheral microcystoid disease does not lead to visual signs and symptoms unless the cysts coalesce to form a retinoschisis in the outer plexiform layer.

Light-induced retinopathy, photic retinopathy (Fig. 11.18)

- Retinal phototoxicity with apoptosis of photoreceptors is well documented in dogs and rodents
- Depending on the duration, intensity and wavelength of light, and degree of ocular pigmentation, phototoxicity can be induced in many species

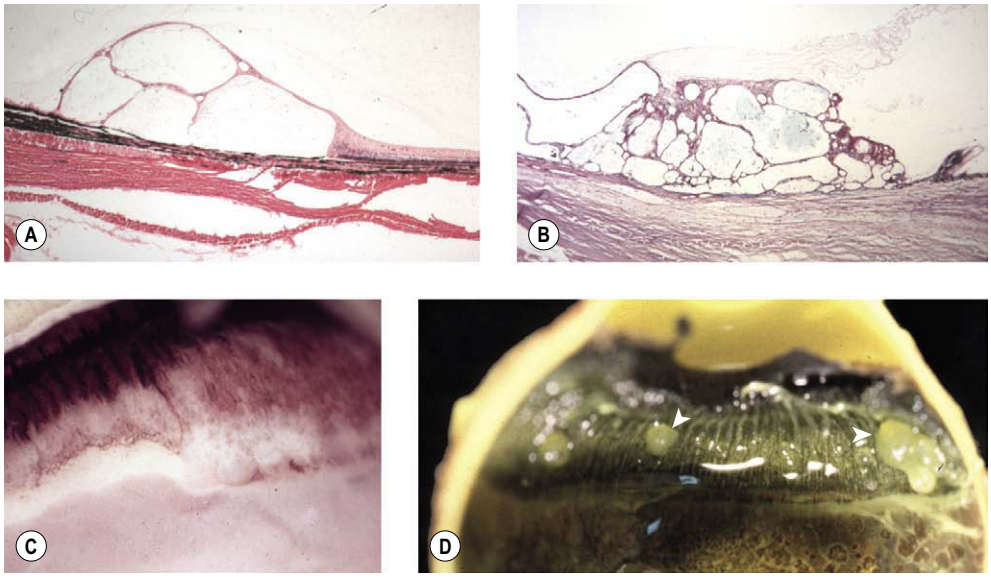


Figure 11.16 Incidental cystic change. (A) Photomicrograph showing the common and inconsequential age-related peripheral cystoid change in the dog retina. (B) Photomicrograph showing cystic change in the ciliary epithelium of the feline pars plana. The cysts contain hyaluronic acid (Alcian blue PAS). (C) Gross photograph of a dog eye showing peripheral cystoid retinal change. (D) Gross photograph of an equine globe showing several individual cysts in the pars plana (arrows). This change is also inconsequential.

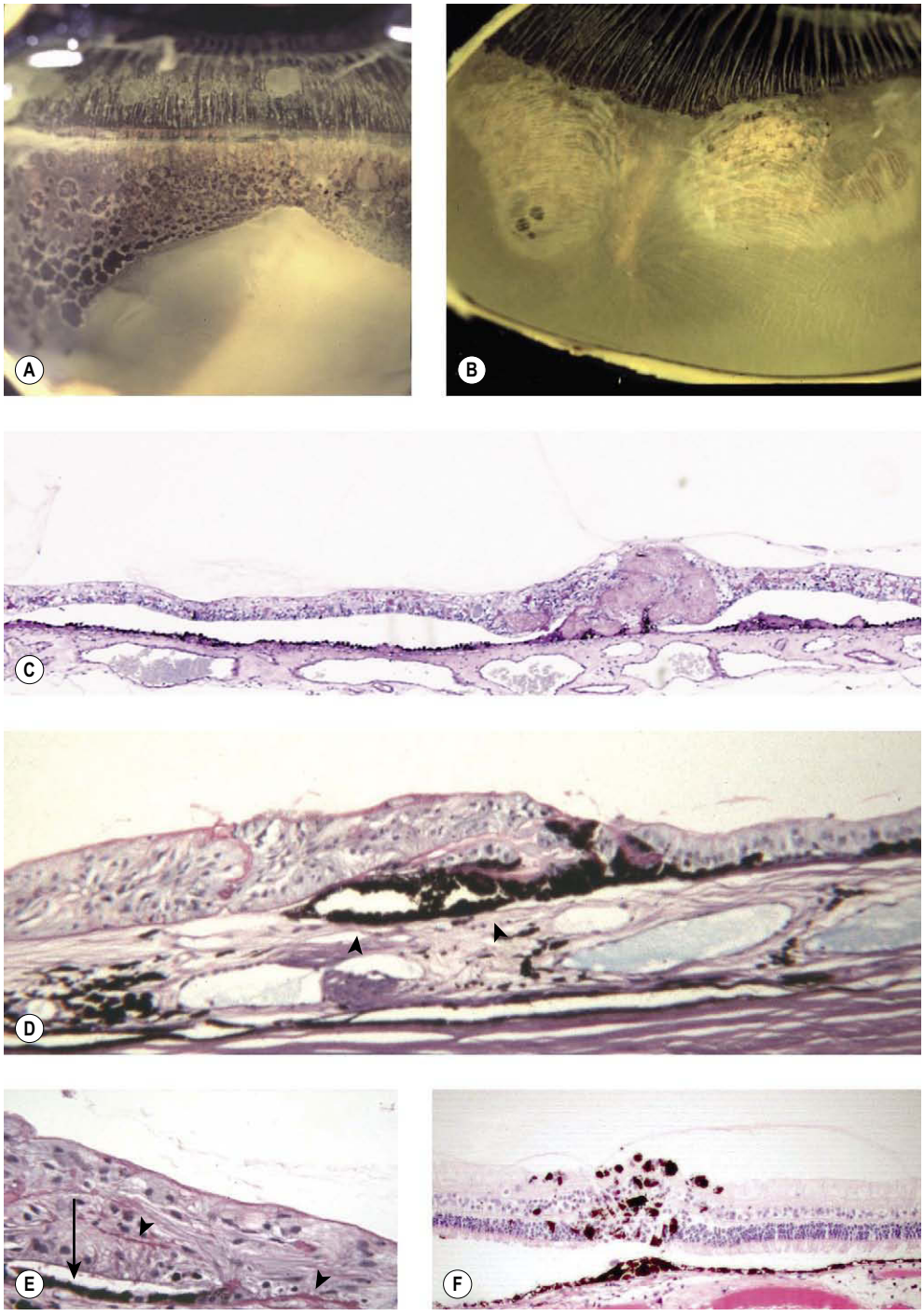


Figure 11.17 Equine senile peripheral retinal degeneration. (A,B) Gross photographs of Bouin's-fixed globes from aged horses showing peripheral retinal and pars plana degeneration, characterized by pigmentary changes. (C) Low magnification photomicrograph showing the peripheral retina from an affected horse. There is retinal atrophy and dispersed redundant PAS-positive material (basement membrane) within the atrophic retina. (D) Photomicrograph showing the ora ciliaris retinae and pigmented epithelium from the pars plana extending into the subretinal space in an affected horse (arrows). (E) Higher magnification photomicrograph showing a segment of atrophic and disorganized retina with a combination of redundant PAS-positive material in the retina (arrowheads) and hyperpigmented RPE cells in the expected location (arrow). (F) Photomicrograph of another area in an affected horse showing only segmental hyperpigmented RPE cells, which extend into the retina in association with atrophy.

- Light-induced retinal damage is not commonly recognized, but may be a problem in surgical patients subjected to intense light from an operating microscope for extended periods
- Retinal phototoxicity is manifest as a disorganization and loss of photoreceptor cells in the outer retina
- Vacuolation of RPE cells may also be seen in focal areas of light-induced damage
- The retina overlying the tapetum is generally more severely affected than the retina within the non-tapetal fundus, where the RPE is typically heavily pigmented.

Comparative Comments

- Although no exact counterpart of light-induced retinopathy is described in humans, light does induce photo-oxidative stress in the human retina, and photic retinopathy is a general term used for humans that describes various types of light-related damage to retinal cells, resulting from photochemical, photodynamic, photocoagulative, or even mechanical processes. Light toxicity, in fact, is widely cited as a major pathogenetic mechanism in the etiology of age-related macular degeneration

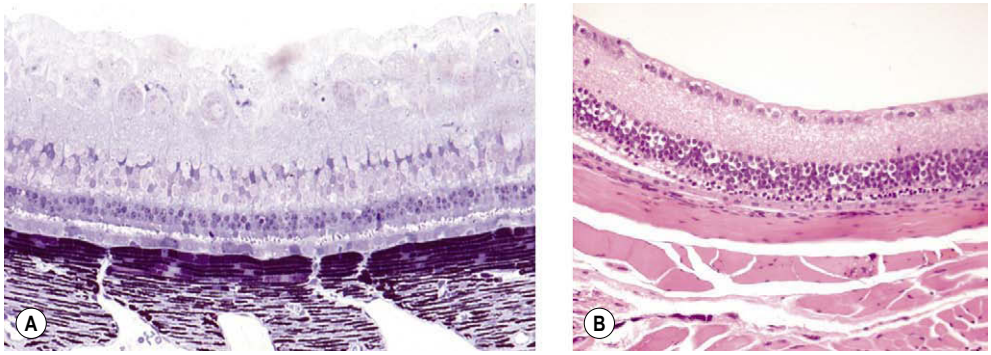


Figure 11.18 Phototoxic retinopathy. (A) Plastic section of a dog retina (Toluidine blue stain). Photoreceptor atrophy was induced experimentally with intense regional light exposure in the anesthetized immobilized eye. (B) Photomicrograph of an albino rat eye from a chronic oncogenicity study. Photoreceptor atrophy is thought to be induced by ambient light levels over the life of the animal. This is a common finding in albino rodents from chronic studies that are housed in institutional lighting.

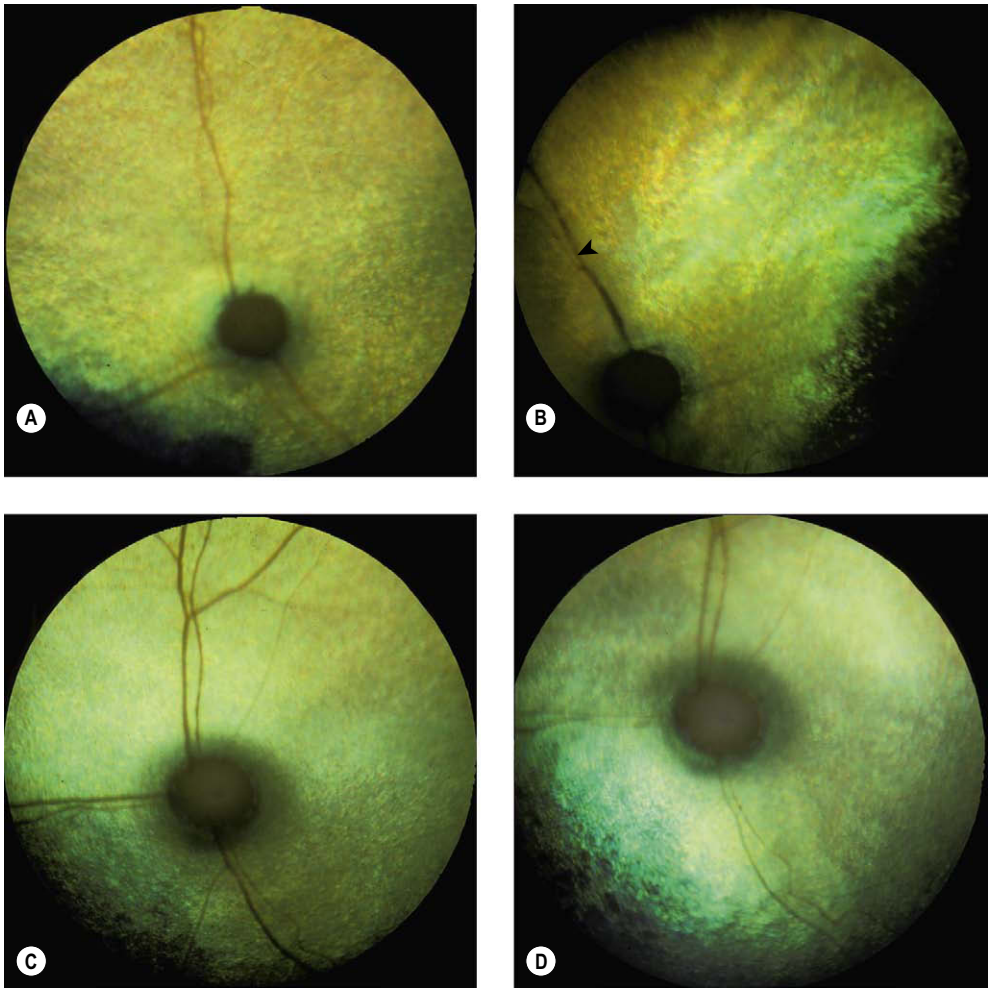


Figure 11.19 Feline fluoroquinolone (Enrofloxacin) retinopathy, fundus. (A) DSH, 14 years old: a generalized atrophy with tapetal hyperreflectivity and attenuation of vessels is present. (B) DSH, 10 years old: the tapetal hyperreflectivity is significant. The superior retinal vein (arrow) is not as attenuated as in the previous case. (C) DSH, 9 years old: tapetal hyperreflectivity and attenuation of vessels are present. Medication was discontinued at this point. (D) This is the same eye as in (C), 9 weeks later. Tapetal hyperreflectivity and attenuation of vessels have progressed despite discontinuing medication.

Comparative Comments (continued)

- Various researchers have emphasized the protective role of melanin granules in the choroid and RPE in preventing retinal damage.

Feline fluoroquinolone-induced toxic retinopathy (Figs 11.19, 11.20)

Acute onset of retinal degeneration has been documented in cats treated with the fluoroquinolone antimicrobial, enrofloxacin.

- After the manufacturer increased the label-recommended dosage of enrofloxacin to a variable range extending up to 20 mg/kg per day as a single or divided dose, reports of sudden blindness in cats started to emerge
  - Since the recommended dose has been subsequently reduced, to no more than 5 mg/kg, the widespread reports of retinal toxicity have stopped
- Diffuse photoreceptor degeneration and acute loss of vision is generally recognizable in affected cats, within days of enrofloxacin administration

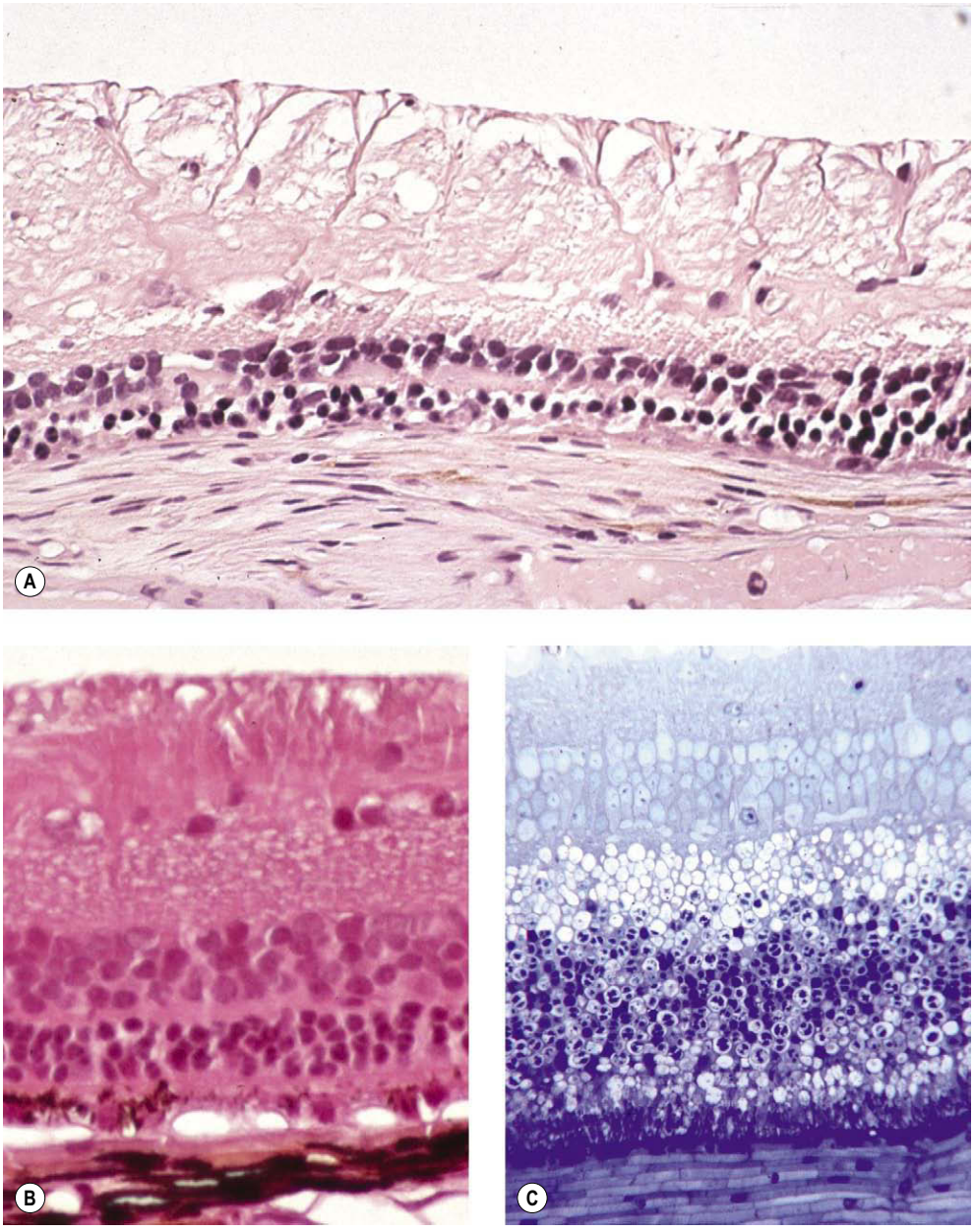


Figure 11.20 Feline fluoroquinolone (Enrofloxacin) retinopathy, pathology. (A) Photomicrograph of the retina from a cat with fluoroquinolone retinopathy in the chronic stages. The eye was removed from the blind cat at necropsy, after the cat died from other causes. (B) High magnification photomicrograph of an affected feline retina showing photoreceptor atrophy in the chronic stages of disease. (C) Plastic section of an experimentally affected cat retina (Toluidine blue stain). Swelling and vacuolar change in the cytoplasm of photoreceptor cells are evident three days after experimental dosing with a fluoroquinolone antibiotic.

- Toxicological studies focused on retinal pathology showed that enrofloxacin at 20 mg/kg per day is toxic to the retina of cats
- Subsequent studies of orbifloxacin have shown similar retinal toxicity but it has never become a clinically significant problem because the recommended dose has remained 'safe'
- Toxicological studies indicate that retinal toxicity is dose- and concentration-dependent. However, it should be borne in mind that animals with renal or hepatic impairment may show signs of toxicity, despite receiving fluoroquinolones at lower than the 'safe' doses established for healthy cats.

Morphologic features of enrofloxacin toxicity

- Acute toxicity is present within hours of a single toxic dose
- The target cell is the rod photoreceptor
- In acute toxicity there is swelling and cytoplasmic vacuolation and in chronic toxicity there is photoreceptor loss.

Plant toxicity

Chronic ingestion of bracken fern (*Pteridium aquilinum*) by sheep in the UK causes diffuse retinal degeneration, termed 'bright blindness.'

This syndrome has been reproduced experimentally and the toxic principle responsible for retinal degeneration shown to be ptaquiloside.

Retinopathy associated with Scrapie in sheep

- Scrapie is a transmissible spongiform encephalopathy, or prion disease, that leads to clinical signs associated with neurodegeneration in affected sheep
- Multifocal circular retinal lesions have been reported in sheep with naturally occurring Scrapie

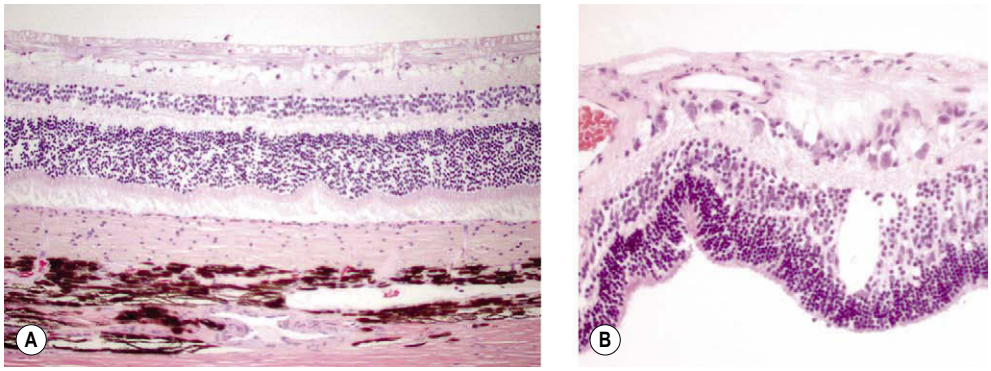


Figure 11.21 Retinal changes in glaucoma. (A) Photomicrograph of a feline retina with glaucoma showing a loss of ganglion cells, but no other changes. (B) Photomicrograph of a canine retina that developed glaucoma after the retina had become detached. The ganglion cells are spared.

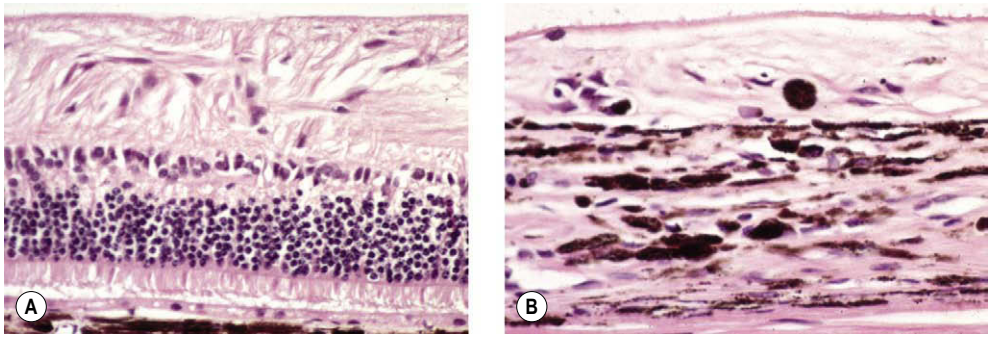


Figure 11.22 Tapetal sparing in canine glaucoma. (A) Photomicrograph showing the tapetal retina from a dog with chronic glaucoma. (B) Photomicrograph showing the non-tapetal retina from the same dog as (A). Relative sparing of the tapetal retina is a common but unexplained feature of canine retinal degeneration in glaucoma.

- Outer plexiform layer atrophy, disorganization and loss of nuclei in both nuclear layers, and Muller cell hypertrophy have been identified in some sheep with naturally occurring Scrapie
- Intense accumulation of abnormal prion protein in the plexiform layers of the retina, and altered expression of immunohistochemical markers for several retinal cell types, in particular increased expression of GFAP, has been reported in experimentally infected sheep.

The retina in glaucoma

The general topic of glaucoma and its affects on the eye will be covered in more detail in Chapter 13 but it is appropriate to comment briefly on the retinal changes seen in glaucoma.

General features of retinal morphology in glaucoma (Fig. 11.21)

- Glaucoma is a disease of the inner retina, particularly the ganglion cells.
  - The pathogenic mechanisms that lead to ganglion cell loss in glaucoma remain unclear
    - A number of different mechanisms have been proposed to account for loss of ganglion cells from the retina, including neurotrophin deprivation and excitotoxicity and an interruption of vascular perfusion in the optic disc
    - An observation made in the COPLOW collection is that in cases where the retina is detached before the development of glaucoma, the ganglion cells are relatively spared.

The canine retina in glaucoma (Fig. 11.22)

- The response of the canine retina to glaucoma differs from that seen in other species
  - This is perhaps related to the acute and extreme nature of intraocular pressure elevation in many affected dogs
  - The entire retina often undergoes necrosis and destruction in canine glaucoma, not just the ganglion cells and inner retina
  - The superior retina is usually less severely affected than the inferior retina in canine glaucoma (so called 'tapetal sparing')
    - This is true even in breeds lacking a tapetum
  - In severe primary glaucoma in dogs, full-thickness retinal necrosis, and subsequent gliosis and atrophy, occurs very rapidly and can reach 'end stage' within a week of the owner first noticing disease in severe and rapidly developing cases. These are the type of cases that are likely to be enucleated.

The retina in glaucoma in cats, and in species other than the dog

Cats, like all other species seen in the COPLOW collection, demonstrate a loss of ganglion cells but, even in chronic and severe glaucoma, the outer retina is generally spared from severe atrophy.

Comparative Comments

- Glaucoma is discussed in greater detail in Chapter 13
- In humans, as well as in most other species, glaucoma is in part a disease of the inner retina, and the discussion regarding the mechanism of ganglion cell loss in glaucoma applies to humans

Comparative Comments (continued)

- The death of ganglion cells is associated with visual field loss and optic atrophy. It is also associated with the thinning of the nerve fiber layer
- Changes in the visual field, appearance of the optic nerve, and thickness of the nerve fiber layer are followed routinely in documenting the progression of glaucoma in human patients.

RETINAL VASCULAR DISEASE

Systemic hypertension

Systemic hypertension is a relatively common, yet probably under-recognized, cause of ocular disease in dogs and cats.

Causes of systemic hypertension in dogs and cats include:

- Secondary:
  - To renal disease
    - Renal disease may also be secondary to hypertension and the cause-and-effect relationship between systemic hypertension and renal disease remains undefined
  - To hyperthyroidism
  - To diabetes mellitus
  - To cardiac disease
  - To hyperadrenocorticism
  - To phaeochromocytoma
  - To carcinoid tumor
  - To hyperaldosteronism
- Primary:
  - Idiopathic or essential hypertension
    - An age-related increase in blood pressure has been documented in both dogs and cats, as well as in humans.

Systemic pathology of hypertension involves a number of target organs:

- Kidney
  - Vasculopathy leads to poor renal perfusion
- Brain
  - Vasculopathy leads to hemorrhage and ischemia
- Eye (Figs 11.23–11.25)
  - The eye is frequently the first organ to manifest clinically apparent complications of systemic hypertension in dogs and cats
  - Hypertensive vasculopathy was diagnosed in 145 canine cases in the COPLOW collection and in 43 feline cases. In

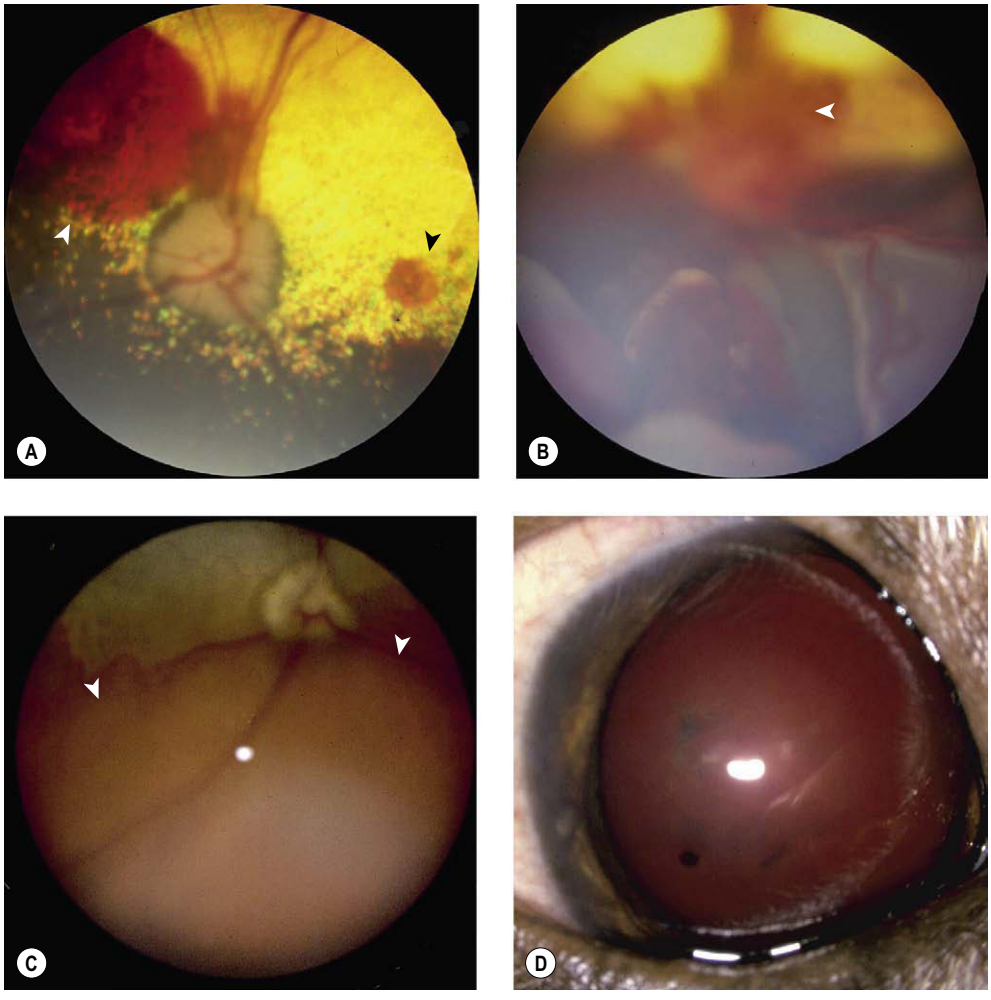


Figure 11.23 Hypertensive chorioretinopathy in dogs, clinical. (A) Cocker Spaniel, 11 years old: intraretinal (black arrow) and a large preretinal hemorrhage (white arrow) are present. (B) Cocker Spaniel, 12 years old: this blind dog has a total inferior retinal detachment. Preretinal hemorrhage can be seen overlying the optic disc (arrow). Intraretinal hemorrhage was also present. (C) Australian Shepherd, 6 years old: the inferior retina is totally detached (arrows) due to subretinal hemorrhage. (D) Brittany Spaniel, 9 years old: the fundus is not visualized due to the massive preretinal hemorrhage.

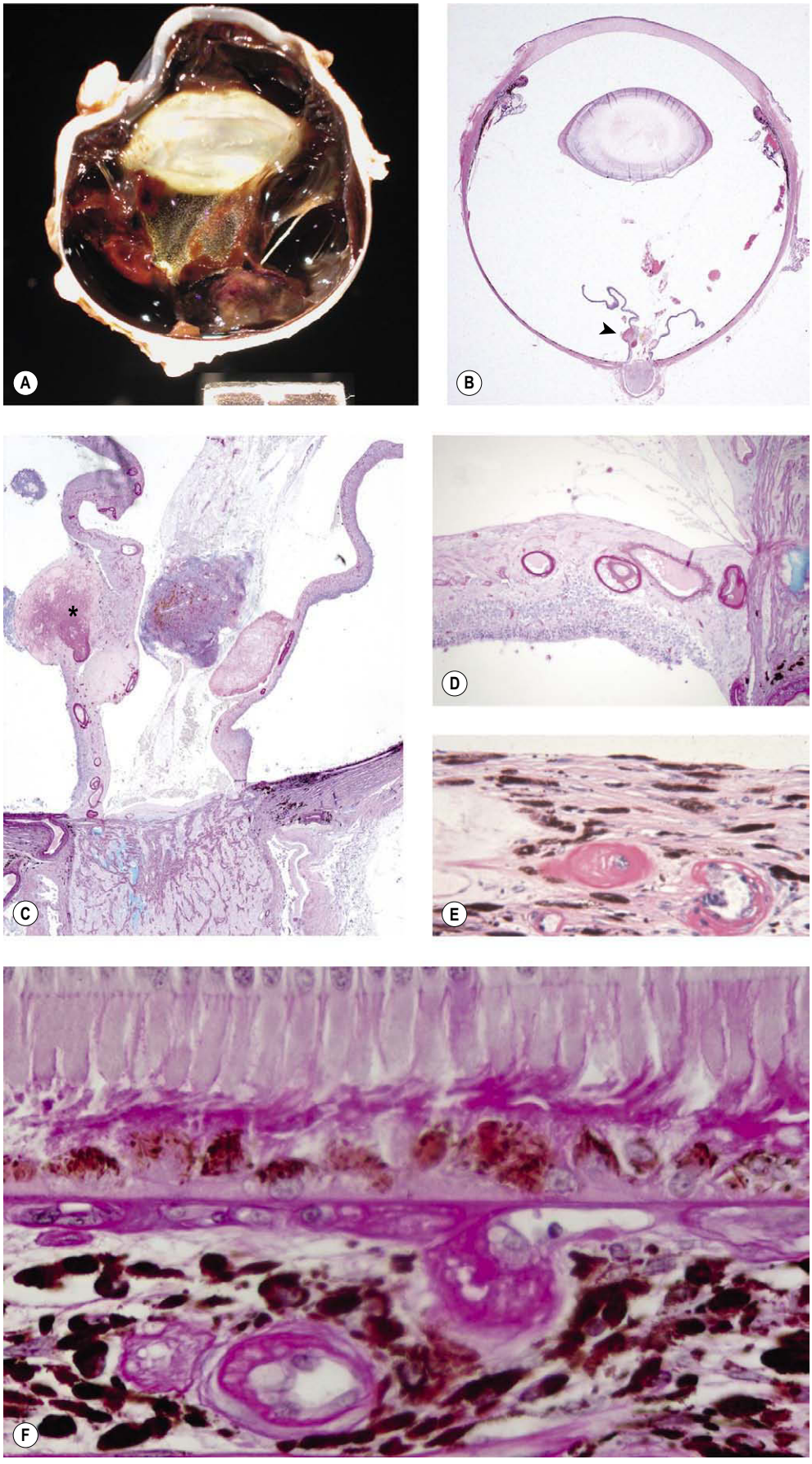


Figure 11.24 Hypertensive chorioretinopathy in dogs, pathology. (A) Gross photograph showing a canine globe with retinal detachment and extensive intraocular hemorrhage characterizing the severe ocular effects of systemic hypertension. (B) Subgross photomicrograph of a canine globe showing hemorrhage, retinal detachment, retinal tear and a focus of fibrin disruption of the retina (arrow). (C) Higher magnification of (B) showing the focus of fibrous disruption of the retina (*), a feature that is usually indicative of systemic hypertension. (D,E) PAS stain showing vascular changes that are typical of systemic hypertension in the retina (D) and choroid (E). (F) Hypertensive vasculopathy in a mandrill affecting the choroidal vessels and the choriocapillaris.

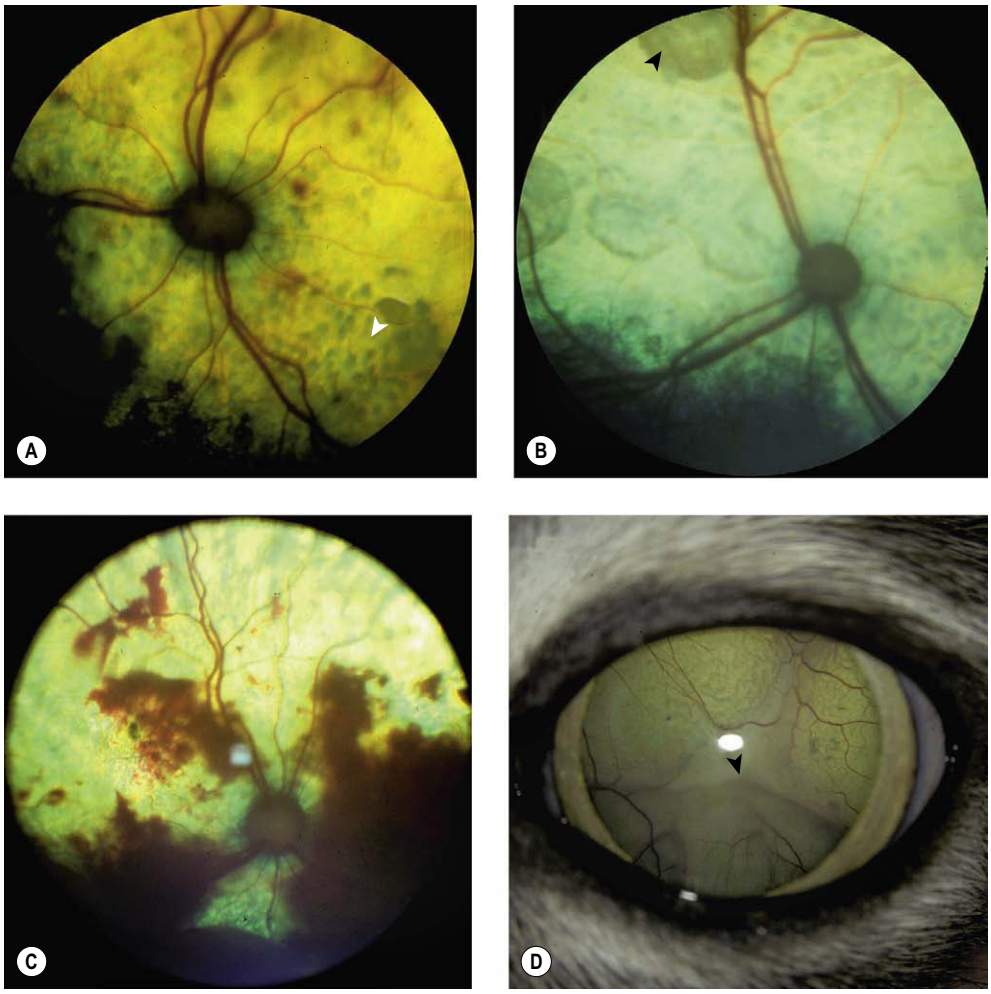


Figure 11.25 Hypertensive chorioretinopathy in cats, clinical. (A) DSH, 13 years old: focal retinal edema is present throughout the fundus (arrow). Pinpoint intraretinal hemorrhages are present to the right of the optic disc. (B) DSH, 10 years old: focal retinal edema and bullous retinal detachments (arrow) are present throughout the retina. (C) Persian, 14 years old: massive intraretinal hemorrhage is present. (D) DSH, 12 years old: subretinal fluid has totally elevated the retina between the ora ciliaris retinae and the optic disc. The optic disc is located below the folds of the bullous retinal detachment (arrow). Retinal vessels can be readily seen through the dilated pupil.

most of these cases hypertension was not suspected at the time of enucleation

- Ocular pathology of systemic hypertension in dogs and cats
  - Lesions are bilateral but not necessarily symmetrical
  - Hypertensive vasculopathy
    - Recognized clinically and grossly by the variations in caliber of individual retinal blood vessels, that may have sections of obliteration and sections of aneurysmal or saccular dilation
    - Vascular lesions are seen in the arterioles of the retina, choroid, or, less frequently, in the iris
    - Diseased arterioles have a thickened vascular profile with decreased luminal diameter
    - Vascular lesions are not consistent throughout the ocular tissues and their identification requires a PAS stain
    - Solid or lamellar PAS-positive deposits, effacing the vessel wall, are associated with fibrinoid necrosis
    - Retinal edema and retinoschisis may be recognized
    - Foci of retinal destruction, including RPE disruption, associated with hemorrhage, fibrin deposition, and neovascular proliferation are a common and distinctive feature of systemic hypertension in the dog and cat retina
  - Intraocular hemorrhage may occur as a direct result of vascular damage
    - Hemophthalmos
    - Intravitreal hemorrhage
    - Retinal hemorrhage
  - Retinal detachment
    - Focal, multifocal or total bullous detachment is a very common feature that reflects hypertensive choroidopathy, with sub-retinal effusion or, in some cases, hemorrhage
    - Pre-iridal fibrovascular proliferation may result, and may contribute to neovascular glaucoma and to distortion of the iris profile
  - Hypertensive optic neuropathy
    - Papilledema may rarely be recognized as a clinical feature in animals with severe hypertension
    - Optic atrophy may result from optic nerve ischemia, particularly in chronic hypertension
    - Hemorrhage in the optic disc secondary to vascular disease is common.

Comparative Comments

- The discussion of the retinal changes due to hypertension in dogs and cats is relevant to the human as well.
- It should be noted, however, that in the human, the pathophysiology of hypertensive retinopathy, optic neuropathy, and choroidopathy remain the focus of sharp controversy.

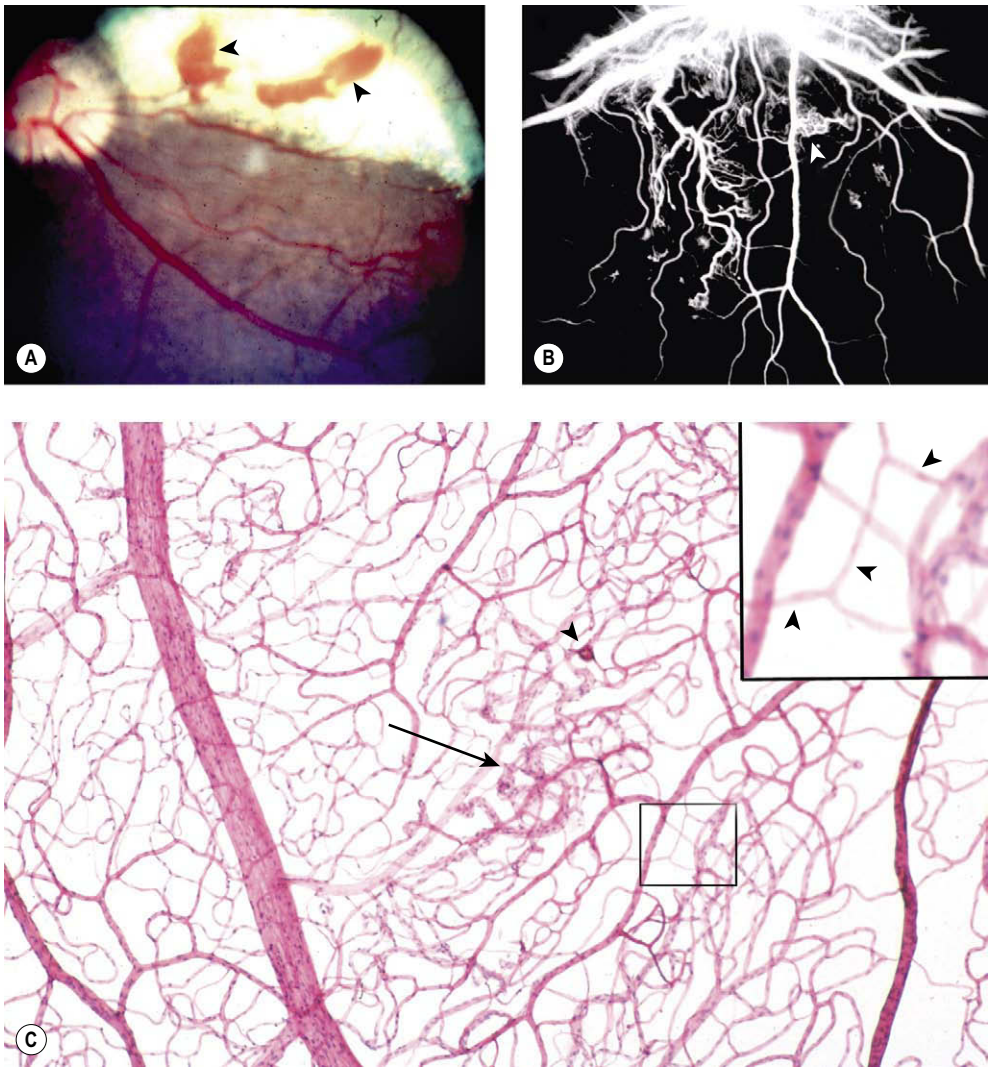


Figure 11.26 Canine experimental diabetic retinopathy (A) Fundus photograph showing retinal hemorrhages (arrows) in an aphakic globe from a dog maintained in an experimentally induced diabetic state for several years. (B) Fluorescein angiogram from experimental canine diabetes showing neovascular foci (arrow). (C) Trypsin digest preparation showing the retinal blood vessels from a dog with experimental diabetes showing a microaneurysm (arrowhead), a neovascular focus (arrow) and the inset shows capillary segments (small arrowheads) devoid of endothelial cells and pericytes. (Courtesy of Ronald Engerman.)

Comparative Comments (continued)

- Some say it is useful in some ways to classify hypertensive retinal lesions into vascular and extravascular, although such a separation is somewhat artificial
- Others, after reviewing experimental and clinical data, proposed dividing hypertensive retinopathy into vasoconstrictive, exudative, sclerotic, and complications of the sclerotic phase, and they have delineated the mechanisms underlying these phases.

Diabetic retinopathy (Fig. 11.26)

- Although previously thought to be uncommon, with longer survival times post-diagnosis, and routine surgical management of diabetic cataract allowing clinical visualization of the fundus, a relatively high incidence of retinopathy is now recognized in dogs with diabetes mellitus
- Spontaneous diabetic retinopathy is seldom associated with clinically apparent loss of vision in dogs
- While the more severe, proliferative form of retinopathy seen in diabetic humans appears relatively uncommon in dogs, 'background retinopathy' with micro-aneurysms in the retinal vasculature and small, focal retinal hemorrhages is commonly seen
- Morphological features identified in dogs with spontaneous or experimentally induced diabetes include:
  - Loss of capillary pericytes
  - Thickening of vascular basement membranes
  - Focal intraretinal hemorrhages
  - Focal areas of degeneration of the neurosensory retina
- Diabetic retinopathy may be complicated by secondary hypertensive vasculopathy in some dogs.

Comparative Comments

- Diabetic retinopathy is of greater significance in human retinal vascular disease than retinal effects of hypertension
- Although the early changes can be induced in animal models, including dogs and rodents, the more advanced changes are limited to humans
- The progressive changes in diabetic humans include capillary basement membrane thickening, loss of capillary pericytes, the development of microaneurysms, intraretinal hemorrhages,

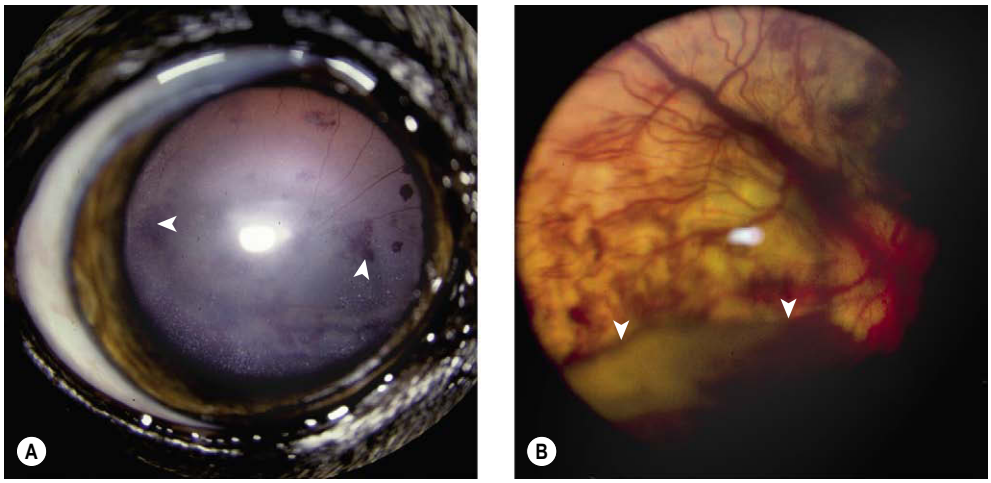


Figure 11.27 Hyperviscosity (A) Mixed Breed, 10 years old: the total protein was 12.9 g/dL. The electrophoresis and associated clinical signs were compatible with the diagnosis. The photograph, representative of both eyes shows intraretinal hemorrhage (arrows) and a total bullous retinal detachment viewed through the dilated pupil. (B) Golden retriever, 9 years old: the total protein was 13.4 g/dL with a total globulin of 12.1 g/dL. The retinal vessels are dilated and multiple intraretinal hemorrhages are present. The inferior retina has a retinal separation and bullous detachment (arrows). The optic disc is poorly seen due to the dilated retinal vessels.

Comparative Comments (continued)

macular edema, and finally the development of proliferative diabetic retinopathy, with glial vascular proliferation occurring as a response to retinal ischemia.

Anemia

Retinal hemorrhage is a recognized complication of profound anemia in cats.

Hyperviscosity syndrome (Fig. 11.27)

Hyperviscosity associated with monoclonal or polyclonal gammopathies, or rarely polycythemia, may lead to a range of ocular abnormalities that are similar to those seen in hypertension, including retinal detachment and retinal and intraocular hemorrhage, as well as secondary glaucoma.

The characteristic feature of hyperviscosity syndrome is pronounced tortuosity and distension of retinal blood vessels, with thrombosis and stasis of blood leading to extreme sacculation of blood vessels.

RETINAL DETACHMENT, RETINAL SEPARATION

Retinal detachment is characterized by the focal or total separation of the neurosensory retina from the underlying RPE. Since the detachment essentially involves separation between the photoreceptor and RPE layers of the retina, rather than actual detachment of the retina in its entirety, including the RPE from the choroid, some prefer the more accurate term, retinal separation, over the more widely used term, retinal detachment.

Factors acting to maintain normal retinal attachment

- The tight junctions of the outer limiting membrane, and the tight junctions of the RPE cells
- The close anatomic relationship between photoreceptor outer segments and the RPE microvillous processes that surround them
- The gentle and widely distributed force exerted by the semi-solid vitreous body on the inner retina.

Factors which can contribute to detachment (Fig. 11.28)

The following contributing factors either predispose to tearing of the retina (i.e. rhegmatogenous detachments), traction on the retina, or serous fluid or inflammatory exudates in the sub-retinal space:

- Advanced retinal degeneration and thinning
- Ocular trauma leading to tearing, necrosis, hemorrhage or vascular leakage
- Inflammation leading to sub-retinal infiltrates, vascular leakage or hemorrhage
- Congenital malformations of the posterior segment including retinal dysplasia, staphyloma and colobomatous lesions (see Ch. 3)
- Cellular bands in the vitreous, segmental vitreal degeneration or dysplasia (as in the Shih Tzu, see Ch. 3), or anterior vitreous prolapse, leading to active or passive traction exerted by the vitreous body on the inner retina
- Neoplasia involving the retina, choroid, anterior uvea, or vitreous cavity, that leads to hemorrhage, vascular leakage, retinal necrosis, or retinal traction
- Stretching of the globe leading to retinal tearing, as may occur in chronic glaucoma
- Toxic conditions that lead to vascular leakage or retinal degeneration
- Vasculopathy that may lead to hemorrhage, leakage or traction
  - Systemic hypertension
  - Diabetes mellitus
  - Hyperviscosity syndrome
  - Thromboembolic disease

Consequences of retinal detachment

- The detached retina ceases to function immediately
  - Retinal metabolism is abruptly lowered
  - The recycling of retinol by the RPE is interrupted
  - The outer retina is separated from its blood supply in the choriocapillaris
  - Gradually there is atrophy of the photoreceptor cells
- The hypoxic retina secretes vascular endothelial growth factor (VEGF), which promotes neovascular proliferation in the iris (pre-iridal neovascular membrane), ciliary body (cyclitic membrane), and optic nerve head. These neovascular membranes have further serious consequences for the function

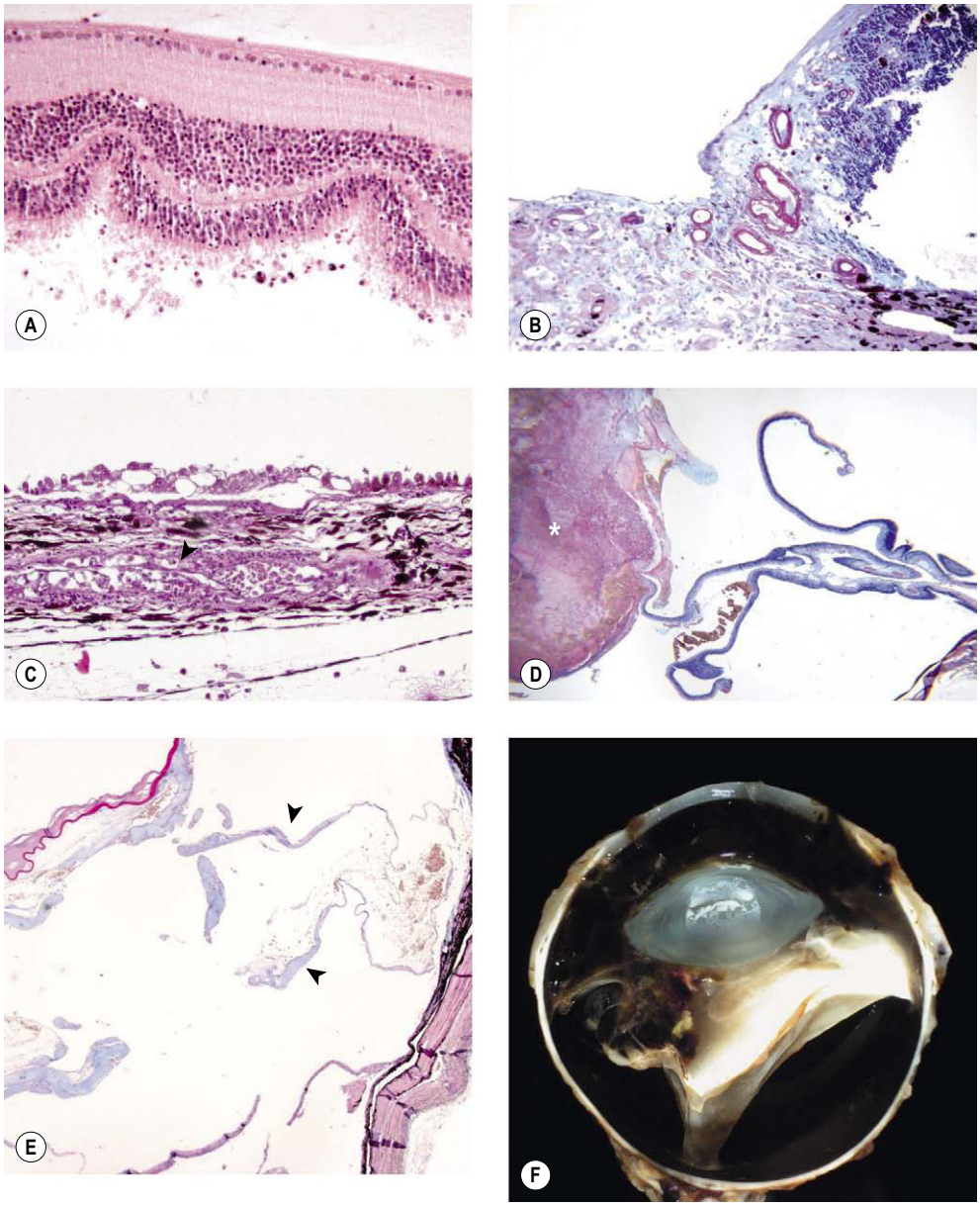


Figure 11.28 Retinal detachment, causes. (A) Photomicrograph of an owl eye showing the detached retina caused by blunt trauma. Phagocytic cells are cleaning up photoreceptor outer segment debris. (B) Photomicrograph of a canine retina near the optic disc showing abnormal blood vessels, with features typical of systemic hypertension (Alcian blue PAS). Vascular leakage is associated with fluid accumulation and retinal detachment. (C) Photomicrograph of a dog choroid and hypertrophied RPE. There is intravascular lymphoma in the choroidal blood vessels (arrow) with edema and retinal detachment. (D) Retinal detachment and retinal tear associated with a large deposit of fibrin and neovascular proliferation (*) associated with systemic hypertension (Alcian blue PAS). (E) Photomicrograph of a dog eye with hypermature, post-traumatic cataract, and numerous cellular strands (arrows) within the vitreous creating traction on the retina and causing detachment. (F) Gross photograph of a dog eye with retinal detachment associated with suppurative vitreitis caused by aspergillosis.

of the eye, including hemophthalmos and secondary glaucoma (see Chs 5 and 9 for more detailed discussion).

Morphologic features of retinal detachment (Fig. 11.29)

- Hemorrhage, protein, inflammation, or other material in the subretinal space
  - The most convincing evidence of pathological retinal detachment is the accumulation of material in the subretinal space, which normally appears optically clear in standard histopathological sections
- Hypertrophy of the adjacent RPE cells
  - Enlargement of cell size along with an inward bulging of the RPE cell apices, often referred to as 'tombstoning'
    - Cell swelling without the characteristic 'tombstoning' can be seen in the absence of pathologic retinal detachment and this can be misleading
  - Sometimes, in cats, the hypertrophied RPE cells will also form complex fronds associated with folding of Bruch's membrane which then bulges into the subretinal space
    - More commonly seen as a pronounced feature in cats
- Outer retinal atrophy
  - Blunting and loss of photoreceptor outer segments
  - Within a few days, apoptosis may be identified in the cells of the outer nuclear layer
  - More profound outer retinal degeneration suggests chronicity, while inner retinal involvement may suggest secondary glaucoma
- Upregulation of vimentin and GFAP expression in the detached retina, beginning within hours of detachment.

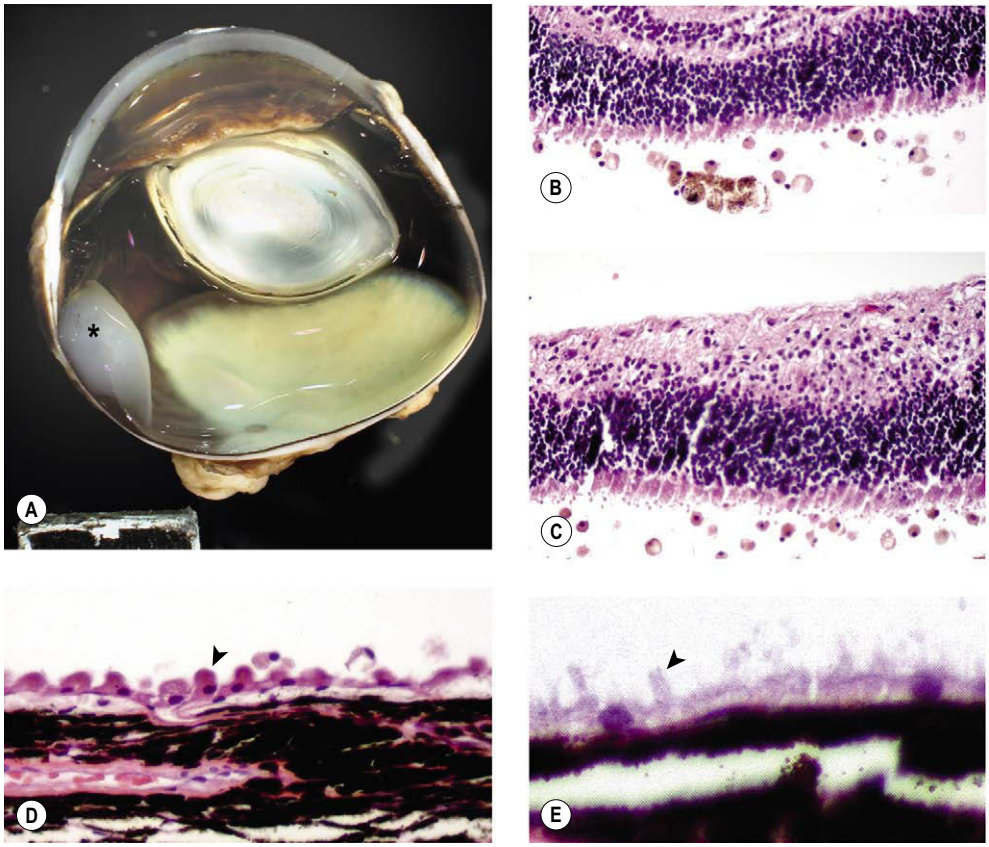


Figure 11.29 Retinal detachment, morphologic features. (A) Gross photograph of a feline eye with serous retinal detachment. There is a protein-rich exudate in the subretinal space (*), which suggests that the detachment is pathologic and not an artifact. (B,C) Photomicrographs showing detached canine retinas with a cellular infiltrate in the subretinal space. (D) Photomicrograph showing hypertrophy and the characteristic rounded apex ('tombstoning') of the RPE (arrow). This change occurs within hours of pathologic retinal detachment. (E) Photomicrograph showing RPE and fragments of photoreceptor outer segments still attached (arrow). They have an appearance somewhat like cilia. This is only seen when the detachment is an artifact of issue processing.

Morphologic features which suggest that retinal detachment is an artifact of tissue processing include:

- Absence of the features described in the previous section
  - However, if one cannot detect the features described above in association with retinal detachment, pathologic detachment cannot be definitively excluded
- Photoreceptor outer segments still attached to the apices of RPE cells in the region of apparent detachment
  - This feature indicates, without doubt, that the apparent retinal detachment is an artifact.

Comparative Comments

The discussion on retinal detachment in non-human species applies to human retinal detachments as well. As indicated in this discussion, retinal detachment corresponds to a separation between the RPE and the neuroepithelium at the junction between the two layers of the optic vesicle, where the embryonic cavity previously existed.

The attachment of the neurosensory retina to the RPE is a tenuous one, dependent on a number of mechanisms including intraocular pressure, vitreous support and pressure, gravity, interdigitation of photoreceptor outer segments and RPE apical microvilli, as well as the interphotoreceptor matrix and adhesion molecules.

The three major types of human retinal detachment are as follows:

1. Rhegmatogenous retinal detachment, the most common type, which results from a collection of vitreous fluid beneath the neural retina through a tear or a hole.
2. Tractional retinal detachment, in which the neurosensory retinal is pulled by intravitreal membranes; this mechanism occurs in proliferative retinopathies such as diabetic retinopathy, sickle cell disease, and retinopathy of prematurity.
3. Exudative, transudative, or hemorrhagic retinal detachment, in which there is an accumulation of subretinal fluid from the choroidal or retinal vessels. This is a mechanism for retinal detachment in choroidal melanomas and inflammatory conditions.

In human eyes with retinal detachment, the principal histopathologic findings are as follows:

- Degeneration of the outer segments and eventual loss of photoreceptor cells
- Migration of Müller cells
- Proliferation and migration of RPE cells
- Development of cystic spaces in the detached retina.

Retinal tear

Many of the same factors that lead to retinal detachment can also lead to a retinal tear.

- Traumatic retinal damage is a leading cause of retinal tears
- Traction on the retina in association with vitreous liquefaction or the formation of contractile vitreous bands is another leading cause of retinal tears
  - Degenerative vitreoretinopathy, as commonly seen in Shih Tzu dogs (discussed in detail in Ch. 3), is often associated with retinal tears

- Retinal necrosis in association with retinal vascular disease is a common cause of retinal tears
  - Vasculopathy associated with systemic hypertension
  - Diabetic vascular disease
  - Atherosclerosis
  - Thromboembolism or embolic metastatic neoplasia.

The morphologic features of retinal tears include (Fig. 11.30)

- Retinal tears usually also imply local or total retinal detachment
- The torn ends of the retina are remodeled by gliosis, such that they take on a rounded and gliotic appearance
- The torn retina often rolls over on itself to adopt a scrolled appearance
  - In the scrolled retina, the outer retina often is in apposition with the inner retina, a configuration that cannot occur unless there is a tear in the retina.

TRAUMA

Retinal contusion, blunt trauma (Figs 11.31, 11.32)

Trauma is frequently suspected as a cause of retinal atrophy, but is difficult to diagnose with certainty because there is seldom an accurate history of trauma.

See Chapter 5 for more detailed discussion of the effects of trauma on the retina.

The morphological features of peracute traumatic retinopathy

- Hemorrhage
- Disruption and fragmentation of photoreceptor outer segments
- Disruption and shattering of the lamellar organization of the retina
- Retinal tear.

The morphologic features of acute traumatic retinopathy

- Apoptosis
- Tissue necrosis or malacia
- Unsupported retinal blood vessels
- Retinal tear.

The morphologic features of chronic traumatic retinopathy

- Gliosis and atrophy
- Unsupported blood vessels
- Retinal tear.

Comparative Comments

- The retinal manifestations of trauma in humans have been extensively studied and categorized
- Direct blunt ocular trauma is the cause of *commotio retinae*, characterized by whitening of the outer retina. Histologically, there is extra- or intracellular edema of the retina, with damage to the photoreceptor cells
- As discussed in regard to other species, direct trauma can lead to traumatic retinal holes, tears, dialysis, and detachment in the human retina.

Lenticular metaplasia in the avian retina (Fig. 11.33)

Metaplastic lens-like differentiation is a common phenomenon in traumatized avian retinas.

Morphologic features of lenticular metaplasia

- Bladder cells or Morgagnian globules found within the atrophic neural retina or retinal pigment epithelium
- Metaplastic lens-like lesions may even demonstrate features consistent with lens capsule
- Gradual transformation from reactive Müller cells to bladder cells, with a change from GFAP to alpha A crystallin expression.

INFLAMMATORY DISEASES OF THE RETINA

Inflammatory disease of the retina seldom occurs in isolation, often being associated with uveal inflammation, due to its close proximity to the choroid, or with inflammatory disease of the central nervous system.

Retinal inflammation attributable to infectious agents

Systemic infections with a wide range of bacterial, viral, fungal, algal and parasitic pathogens may result in retinal inflammation. Many of these pathogens lead to retinal disease secondary to infection being established with the choroid, i.e. by extension of posterior uveitis, and are considered in Chapter 9.

Those pathogens for which the retina may be considered a target tissue are addressed below.

Canine distemper virus (Figs 11.34, 11.35)

- Canine distemper is a Morbillivirus (paramyxovirus) which causes a wide variety of systemic lesions when infecting susceptible dogs or other carnivores
- Retinal disease is seen in association with encephalitis and, although keratoconjunctivitis sicca and blinding optic neuritis may occur, frequently there are no ocular signs other than the typical ophthalmoscopic findings of multifocal retinitis or chorioretinitis

Morphologic features of canine distemper retinitis

- Grossly, there are multifocal, perivascular areas of retino-choroidal involvement which may appear pale, pigmented, or atrophic
- Histologically, in active infection, retinal disorganization, eosinophilic intranuclear or intracytoplasmic inclusion bodies, and multi-nucleate syncytia are observed

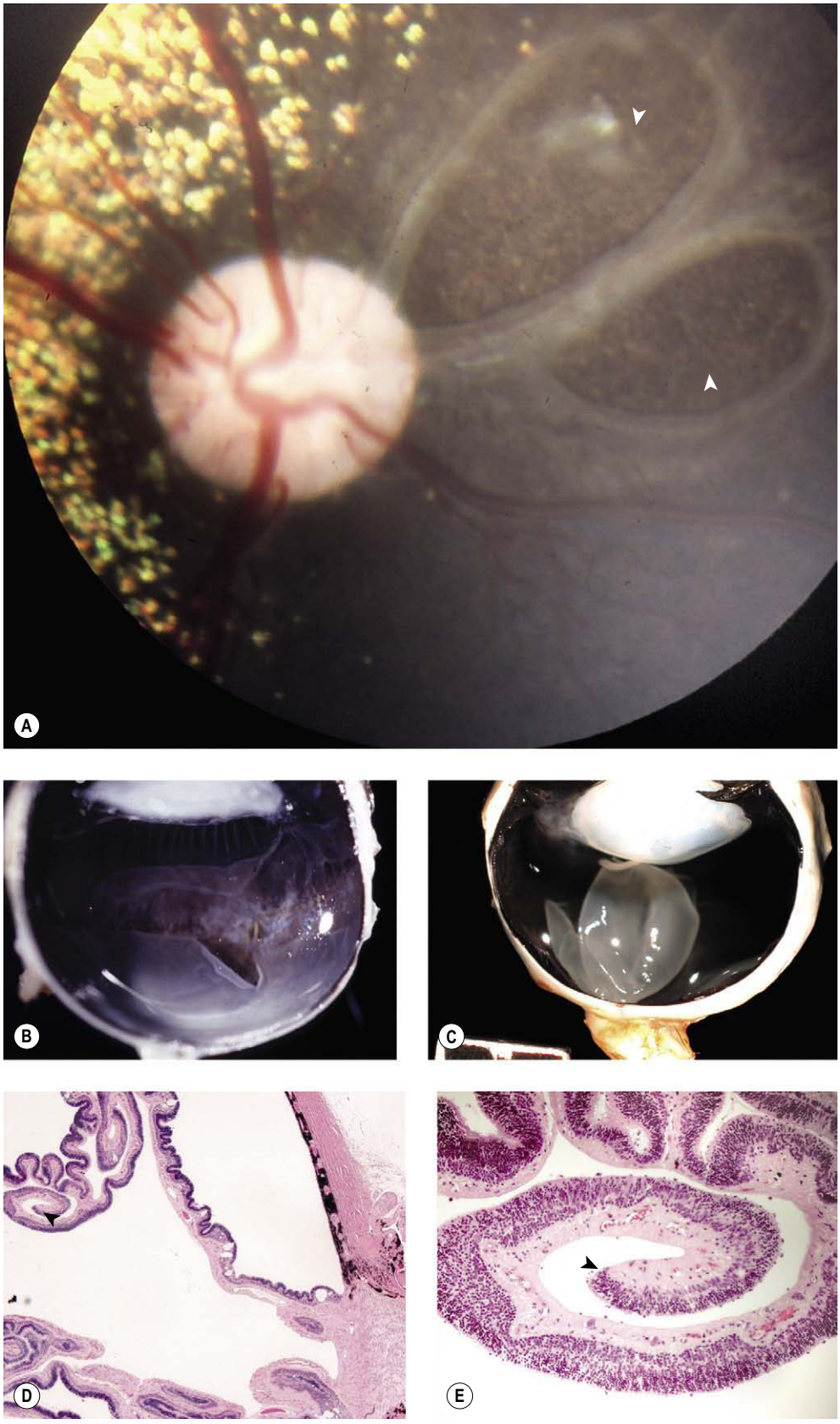


Figure 11.30 Retinal tear. (A) Shih Tzu, 6 months old: two holes in the retina (arrows) with perilesional edema are present. (B) Gross photograph of a Shih Tzu eye showing a peripheral retinal tear. (C) Gross photograph of another Shih Tzu dog with giant retinal tear 360°. (D,E) Photomicrographs at two magnifications of the same Shih Tzu as B showing the rounded edge (arrow) characteristic of a retinal tear that has had time to form a glial scar.

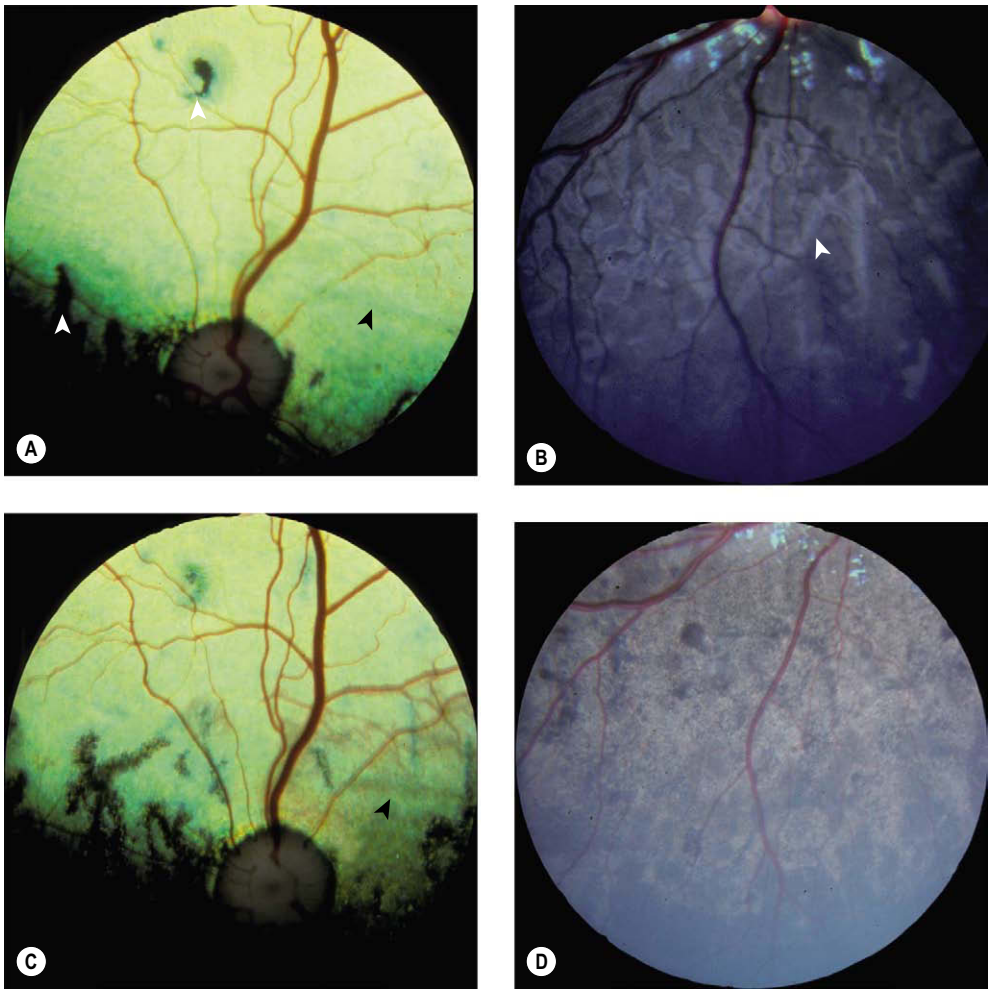


Figure 11.31 Trauma to the retina, fundus. (A) Beagle, 1.5 years old: this dog was still blind 1 week after being hit by a car. The photograph is of the tapetal retina. Linear areas of retinal edema (black arrow) and focal areas of abnormal pigment and edema (white arrows) are present. (B) Non-tapetal retina of the same eye as in (A) showing multiple areas of retinal edema (arrow). (C) The tapetal retina of the same eye as in (A) taken 1 week later. Increased tapetal pigmentation is present. The tapetum is now hyperreflective in the areas of previous retinal edema (arrow). (D) This is the non-tapetal retina of the same eye as in (A) taken 1 week later. Retinal edema has resolved, leaving areas of depigmentation and pigment clumping.

- In chronic disease, retinal atrophy and gliosis are seen, along with migration of pigment epithelial cells into the neurosensory retina.

Bovine thromboembolic meningoencephalitis, *Haemophilus somnus* infection (Fig. 11.36)

- *Haemophilus somnus* is a Gram-negative bacterial pathogen of cattle, which can affect the urinary, reproductive, or respiratory tracts leading to serious disease
- The brain and the eye become affected as a result of widespread septic vascular thromboembolism
- Ocular signs, although striking, are generally a minor clinical concern because of the rapidly fatal nature of the embolic form of the disease

Morphologic features of retinal disease

- There is focal or multifocal acute hemorrhagic and necrotizing retinitis associated with septic vascular thromboemboli and vasculitis.

Herpes viral retinitis in camelids (Fig. 11.37)

- Infection with equine herpesvirus-1 can cause clustered outbreaks of encephalitis and retinitis in camelid species that are in contact with *Equidae*
- Potentially fatal encephalitis is associated with neurologic signs and with vision loss in one or more animals

Morphologic features of retinitis in affected animals

- Acute necrotizing retinitis
- Eosinophilic intranuclear inclusion bodies.

Bovine virus diarrhea (BVD) virus in cattle (Fig. 11.38)

- Calves infected with BVD virus *in utero*, may be affected with a syndrome that includes cerebellar hypoplasia, microphthalmia, and retinal disorganization and dysplasia (see Ch. 3)

Morphologic features of retinal disease associated with pre-natal BVD infection

- Retinal folds or rosettes
- Loss of lamellar retinal organization
- Retinal gliosis
- Segmental loss of RPE cells or spindle cell metaplasia of RPE cells.

West Nile virus in raptors (Fig. 11.39)

- West Nile virus has a high morbidity in avian species, with a highly variable mortality between affected species

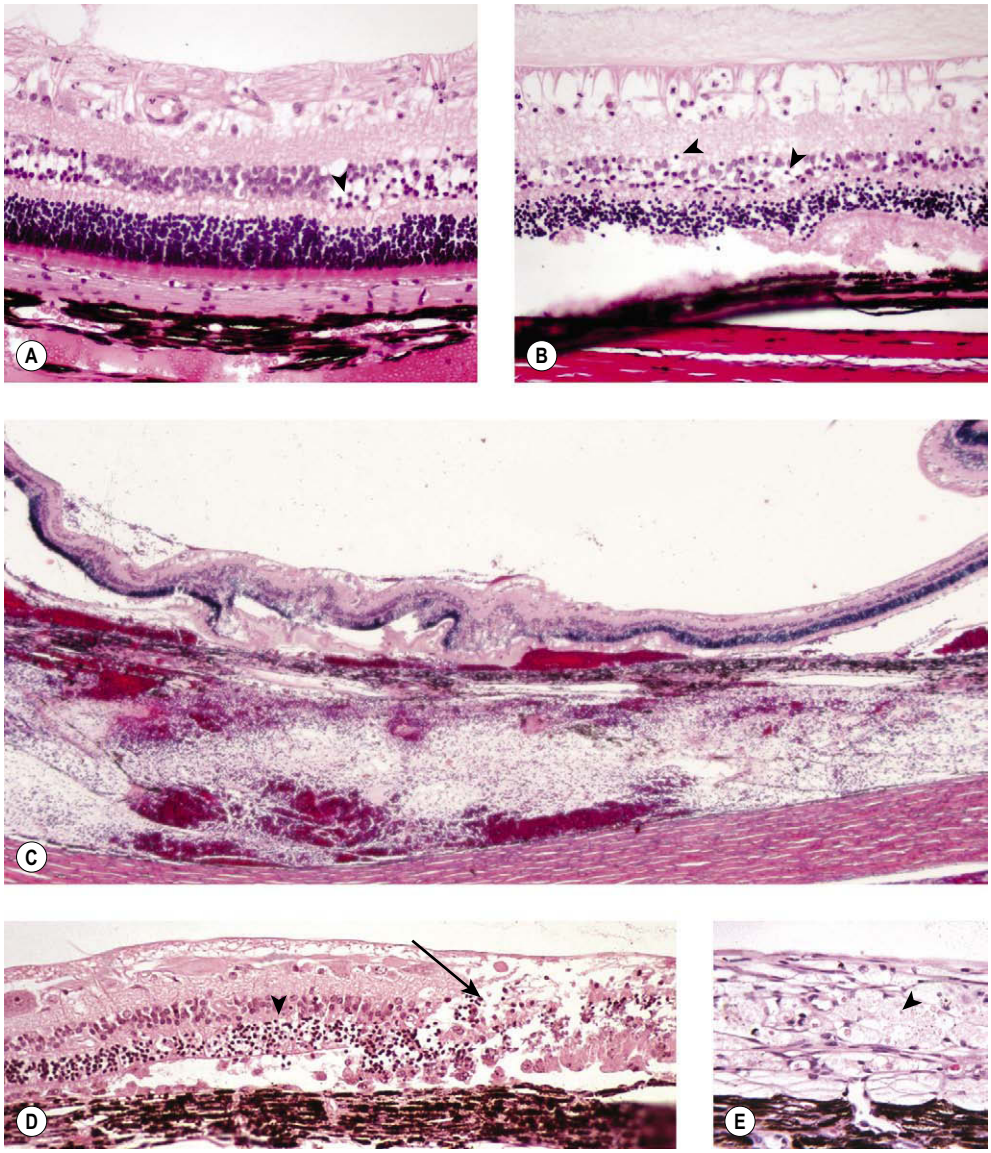


Figure 11.32 Trauma to the retina, pathology. (A,B) Photomicrographs, from two dogs who died within hours after head trauma, showing regionally variable apoptosis in the retina (arrows). (C) Low magnification photomicrograph showing the retina from a dog that had its eyes removed within hours after a traumatic penetrating wound caused by a BB. Notice the segmental disruption and hemorrhage. (D) Photomicrograph of a dog eye, that was removed several days after blunt trauma, showing atrophy and apoptosis in one segment (arrowhead) and necrosis and phagocytosis in another segment (arrow). (E) Photomicrograph of the retina from a dog that was necropsied 10 days after severe head trauma, showing end-stage retinal atrophy. However, there are still phagocytic cells in the gliotic remnants of the retina (arrow).

- Raptors have a fairly high morbidity, and mortality is often associated with vision loss secondary to retinal or uveal infection

Morphologic features of West Nile Virus infection in the raptor eye

- Multifocal retinal or uveal lymphocytic infiltration
- Segmental retinal necrosis, or atrophy and gliosis.

Toxoplasmosis

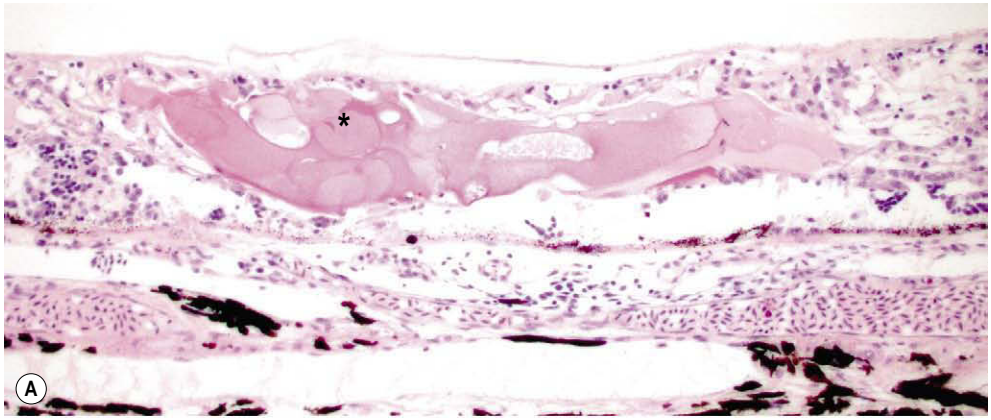
- Active, disseminated infection with Toxoplasma gondii is reported to result in a characteristic multi-focal chorioretinitis in affected animals, however, there are no cases of chorioretinitis associated with toxoplasmosis in the COPLOW collection
- In contrast to humans, in which the retina appears to be a target tissue, in domestic species, retinitis tends to occur by extension of inflammation from the adjacent choroidal tissue
- The pathogenesis of ocular toxoplasmosis is discussed in greater detail in Chapter 9.

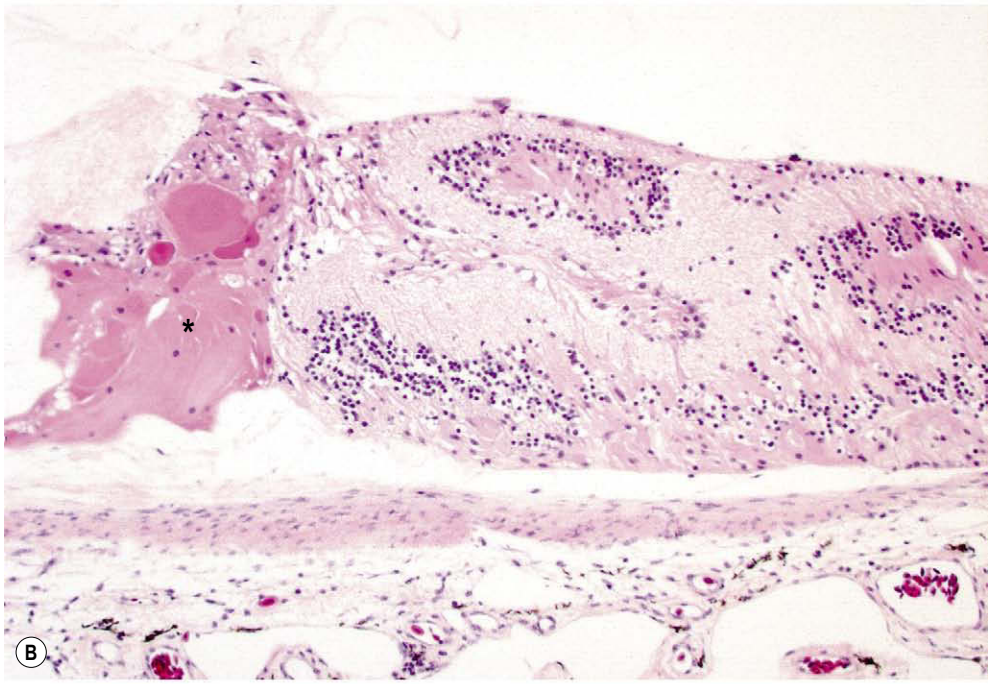
Toxocara canis ocular larva migrans (Figs 11.40, 11.41) (see also Ch. 9)

Young dogs raised under conditions that promote a heavy exposure to infectious eggs, are at risk of developing inflammatory ocular disease associated with the migration of larval nematodes through ocular tissues, including the retina and uvea causing retinitis and uveitis, respectively.

Morphologic features of canine ocular larval migrans

- The hallmark feature of infestation is a migration tract with associated granulomatous inflammation which undulates through the uvea, retina, and vitreous
- The focal granulomas often need to be identified during gross examination with magnification, and the tissues embedded and





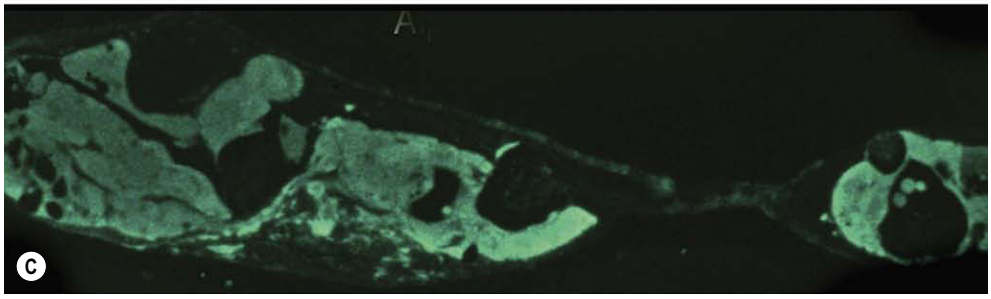


Figure 11.33 Trauma to the retina in birds, lenticular metaplasia. (A) Photomicrograph of the traumatized retina from a Red-tailed hawk showing end-stage retinal atrophy and focal lenticular metaplasia (*), a common phenomenon in retinal degeneration and gliosis in bird eyes. (B) Photomicrograph of another hawk eye with post-traumatic retinal degeneration and lenticular metaplasia (*). (C) Immunofluorescence photomicrograph of another bird retina showing the lenticular metaplasia staining positive for alpha crystallinue.

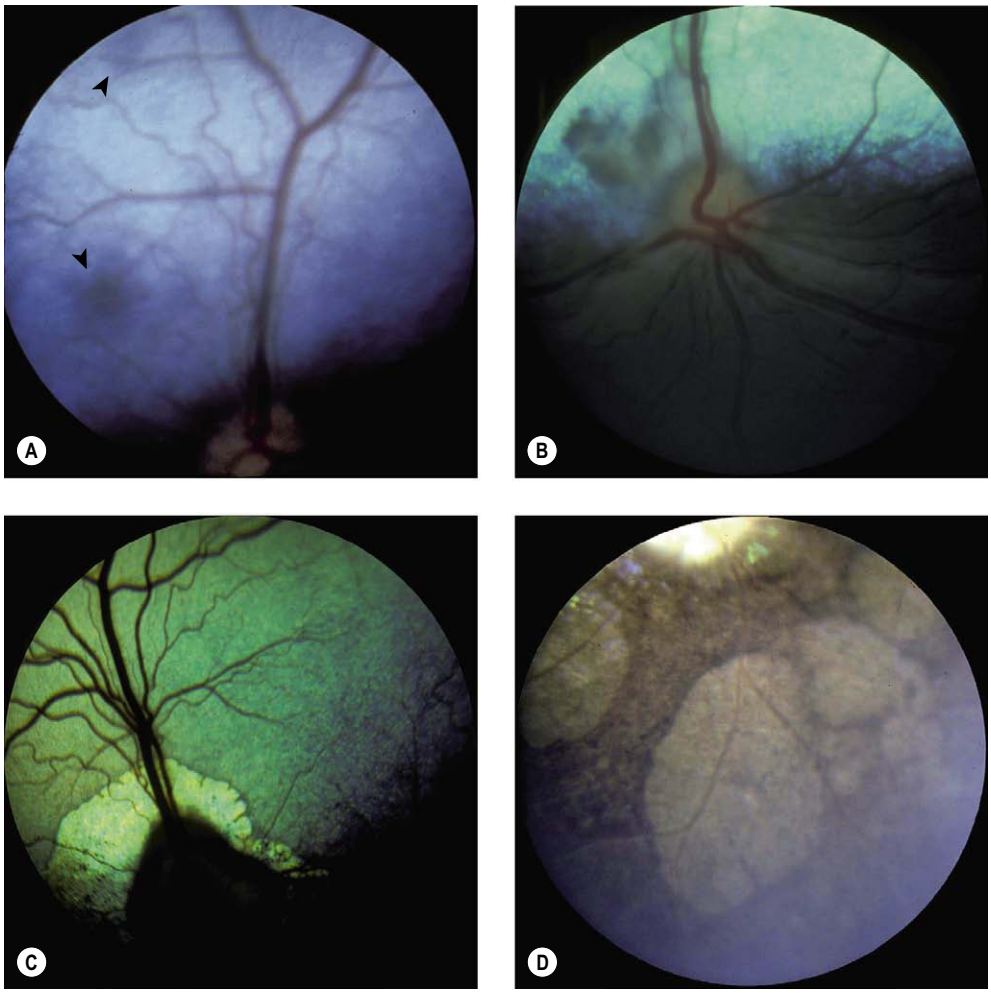


Figure 11.34 Canine distemper retinopathy, fundus. (A) Doberman Pinscher, 8 weeks old: focal areas of retinal edema (arrows) were presumed to be associated with distemper in this unvaccinated puppy with respiratory disease. (B) Beagle, 6 months old: areas of retinitis with indistinct borders are present in the peripapillary retina. Optic neuritis is also present in the unvaccinated dog with a history of recent seizures. (C) Norwegian Elkhound, 4 years old: the peripapillary retinal atrophy and kerito conjuctivity sicca are compatible with previous active distemper. (D) Mixed Breed, 6 years old: the large areas of depigmentation are compatible with prior distemper retinitis. This dog was currently having seizures.

sectioned in such a way that the lesions are isolated for histologic evaluation
- Eosinophils are seldom a prominent feature of ocular larval migrans in dogs
- A high degree of suspicion is warranted on finding unexplained retinal perivascular lymphocytic inflammation in young dogs.

Comparative Comments

Concerning ocular inflammation attributable to infectious agents, the human retina is involved in instances of infectious endophthalmitis secondary to bacterial or fungal disease.
- Fungal infections of the retina occur in immunosuppressed human patients as a result of fungemia. The most commonly implicated fungi are *Candida, Aspergillus*, and *Cryptococcus neoformans*
- A number of viruses can affect the human retina, including herpes simplex, herpes zoster, cytomegalovirus, human immunodeficiency virus (HIV), rubella, and measles
  - *Herpes simplex, Herpes zoster* and *cytomegalovirus* can cause a devastating destruction of the human retina, known as acute retinal necrosis.

RETINAL NEOPLASIA

Primary neoplasms of the retina

These are rare in domestic animals. There are 13 cases of primary retinal tumors in dogs and two in cats in the COPLOW collection.

Canine retinal glioma (astrocytoma) (Figs 11.42, 11.43)

There are 10 examples in the COPLOW collection
- Although not common, GFAP-positive gliomas are the most frequently encountered primary retinal tumors in dogs
- Retinal gliomas most often arise in the central retina, near or continuous with the optic nerve
- Gliomas can have a bland or an anaplastic cellular profile (see Ch. 12). The anaplastic tumors are often extensively necrotic.

Retinal tumors with features of neural differentiation

Primitive neuroectodermal tumors (PNET), including medulloepithelioma and retinoblastoma (Fig. 11.44).
- PNET are usually in the peripheral retinal or continuous with the ciliary body

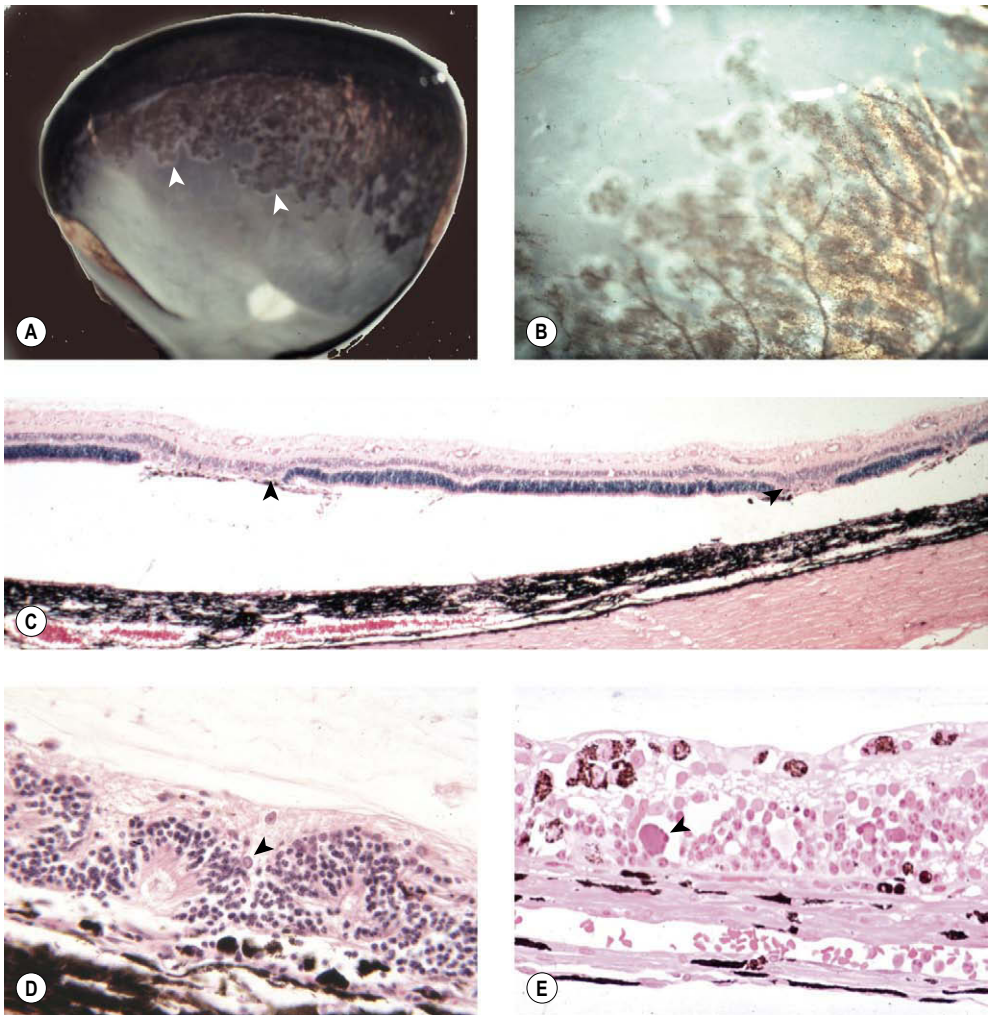


Figure 11.35 Canine distemper retinopathy, pathology. (A) Gross photograph showing the retinal surface from a posterior segment with coalescing foci of degeneration and pigmentation (arrows). (B) Magnified view of the same specimen as (A) showings the affected portion of the retina in more detail. (C) Low magnification photomicrograph showing multiple foci of retinitis and retinal degeneration (arrows) in canine distemper retinitis. (D,E) Higher magnification photomicrographs showing a combination of retinal degeneration, pigment invasion and minimal inflammation. Intranuclear inclusions are seen in both photographs (arrows).

- PNET have been reported in a number of different species including dogs, horses and camelids
- Medulloepithelioma is characterized by the presence of thick tubular rosettes with a complex multi-cell lining and a distinct lumen. More simple Flexner–Wintersteiner or Homer–Wright rosettes may also be present in medulloepithelioma, but they are not the defining feature
  - Most medulloepithelial tumors originate in the ciliary body or optic nerve, rarely in the retina
- Retinoblastoma in animals (Fig. 11.45)
  - Most PNET tumors of animals do not satisfy the rather stringent criteria to be categorized as retinoblastoma. There is one canine case in the literature, which has been designated as a retinoblastoma using criteria developed in humans
  - Retinoblastoma is a PNET of the retina with the following features:
    - Poorly-differentiated, very primitive neural cells, with a large nucleus to cytoplasm ratio
    - Simple rosette structures with characteristics of either Flexner–Wintersteiner or Homer–Wright
      - Flexner–Wintersteiner rosettes are characterized by a single layer of cells with apical tight junctions and a distinct lumen
      - Homer–Wright rosettes are characterized by a more primitive and less distinct structure with no tight junctions and an indistinct lumen
      - Although rosette structures are a frequent feature of retinoblastoma, their presence is not required to make the diagnosis
    - Sparse vascularity and associated extensive tumor necrosis, except immediately around blood vessels
    - Mineralization within human retinoblastoma is so common that it is a feature that is essential to make the diagnosis by ultrasound or CT scan.

Comparative Comments

- In humans, the most common primary intraocular malignancy of childhood is retinoblastoma. This tumor occurs in approximately 1 in 14 000–20 000 live births
- The tumor is composed of small dark cells, with hyperchromatic nuclei and scanty cytoplasm. Rosettes (Flexner–Wintersteiner and Homer–Wright) are characteristically seen
- A benign form of the tumor, known as retinocytoma, can occur
- Retinoblastoma is extremely rare in other species
- Other tumors of the human retina are uncommon and include massive gliosis of the retina, astrocytic hamartomas, hemangioblastomas, as well as adenomas and adenocarcinomas of the RPE.

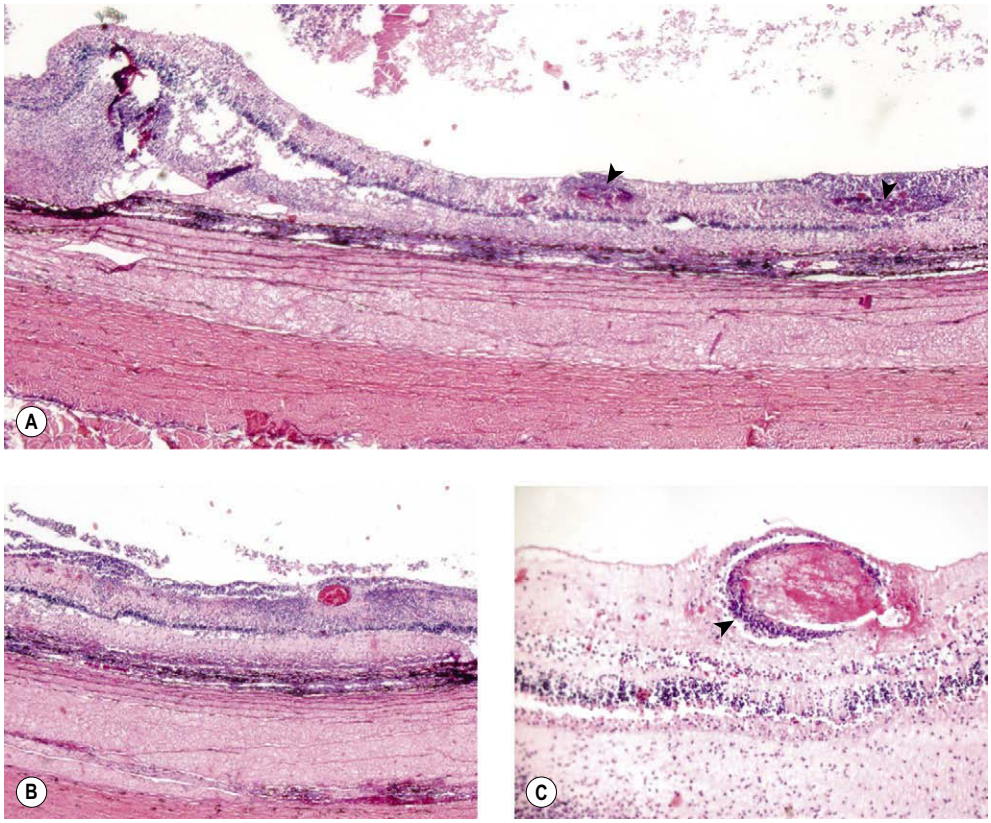


Figure 11.36 *Haemophilus somnus* Retinitis. (A) Low magnification photomicrograph of a bovine retina with multifocal thrombotic blood vessels (arrows) and suppurative retinitis typical of disseminated *Haemophilus somnus* infection. (B,C) Higher magnifications of the same case as (A) showing more detail of the retinitis (arrow).

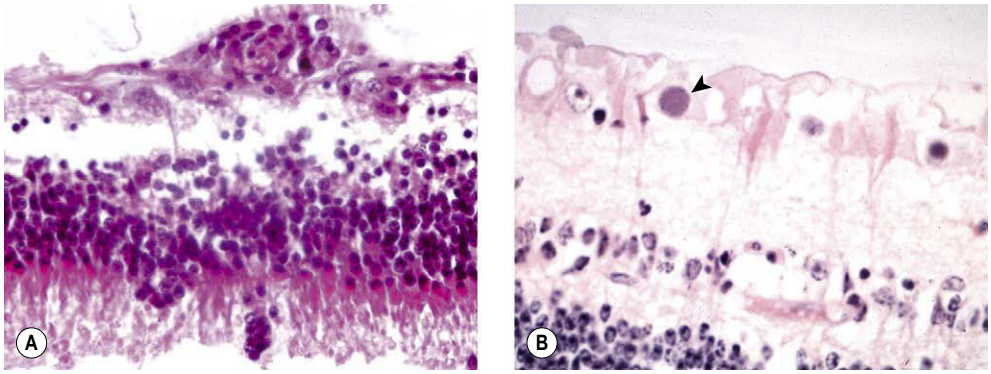


Figure 11.37 Retinitis associated with herpesvirus in camelids. (A,B) Photomicrographs of the retina from a llama showing retinitis, edema and degeneration caused by infection with herpesvirus. Typical herpes viral intranuclear inclusion bodies (arrow) can often be found.

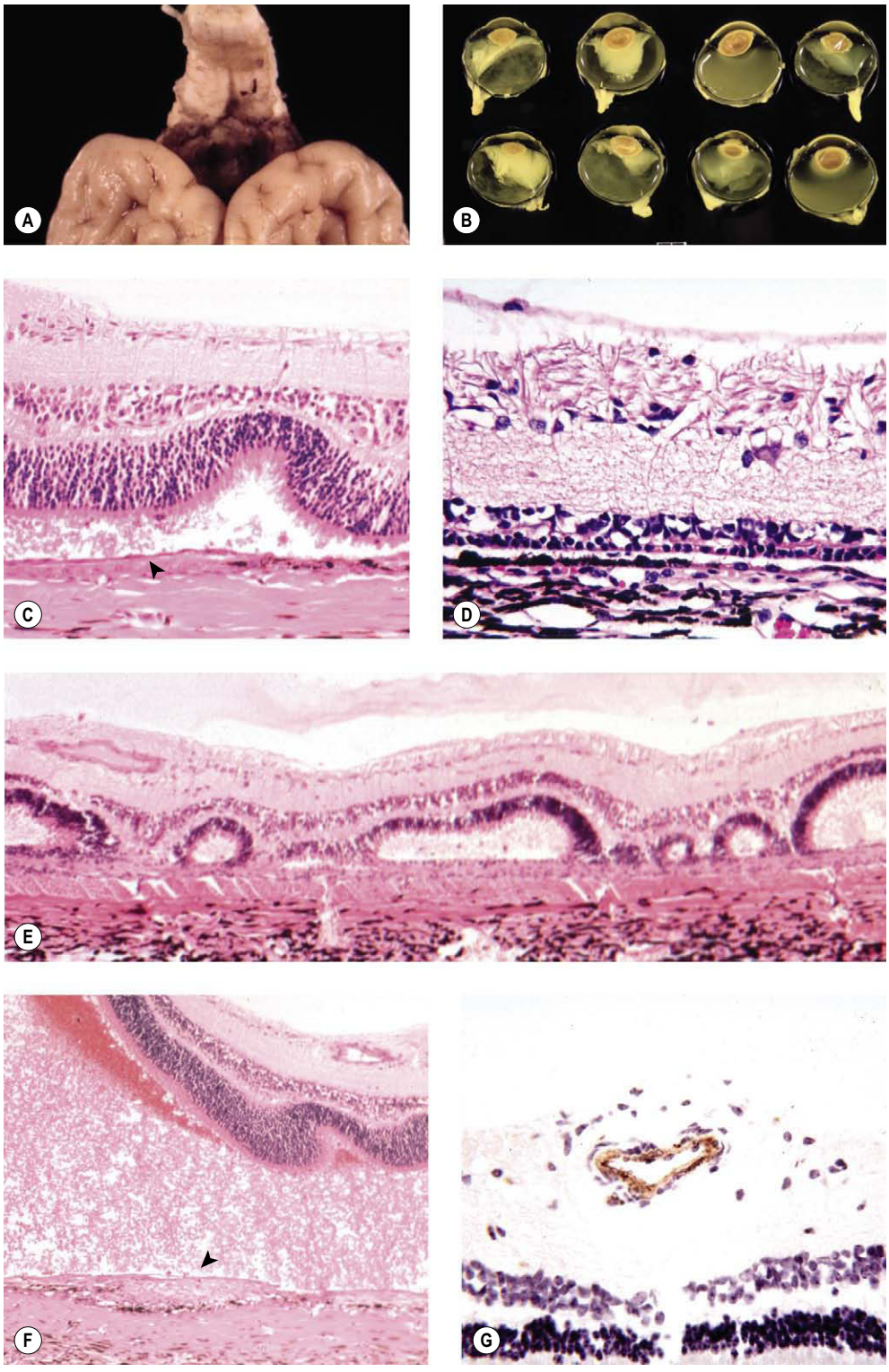


Figure 11.38 Retinopathy associated with intrauterine bovine viral diarrhea (BVD) Infection. (A) Gross photograph of a neonatal calf brain showing cerebellar hypoplasia resulting from *in utero* infection with BVD virus. (B) The gross montage image shows a series of eight Bouin's-fixed globes, from four neonatal calves euthanized because of congenital BVD, with microphthalmos and excess protein in the vitreous. (C) Photomicrograph of the retina and choroid from an affected calf showing retinal detachment and a spindle cell membrane lining the inner choroid (arrow). (D) Photomicrograph showing outer retinal degeneration and atrophy. (E) Low magnification showing multifocal retinal involvement in an affected calf. (F) Spindle cell membrane on the inner aspect of the choroid at the level of the choriocapillaris (arrow) is a common feature in ocular involvement by congenital BVD. (G) Immunohistochemistry showing BVD antigen in retinal blood vessels.

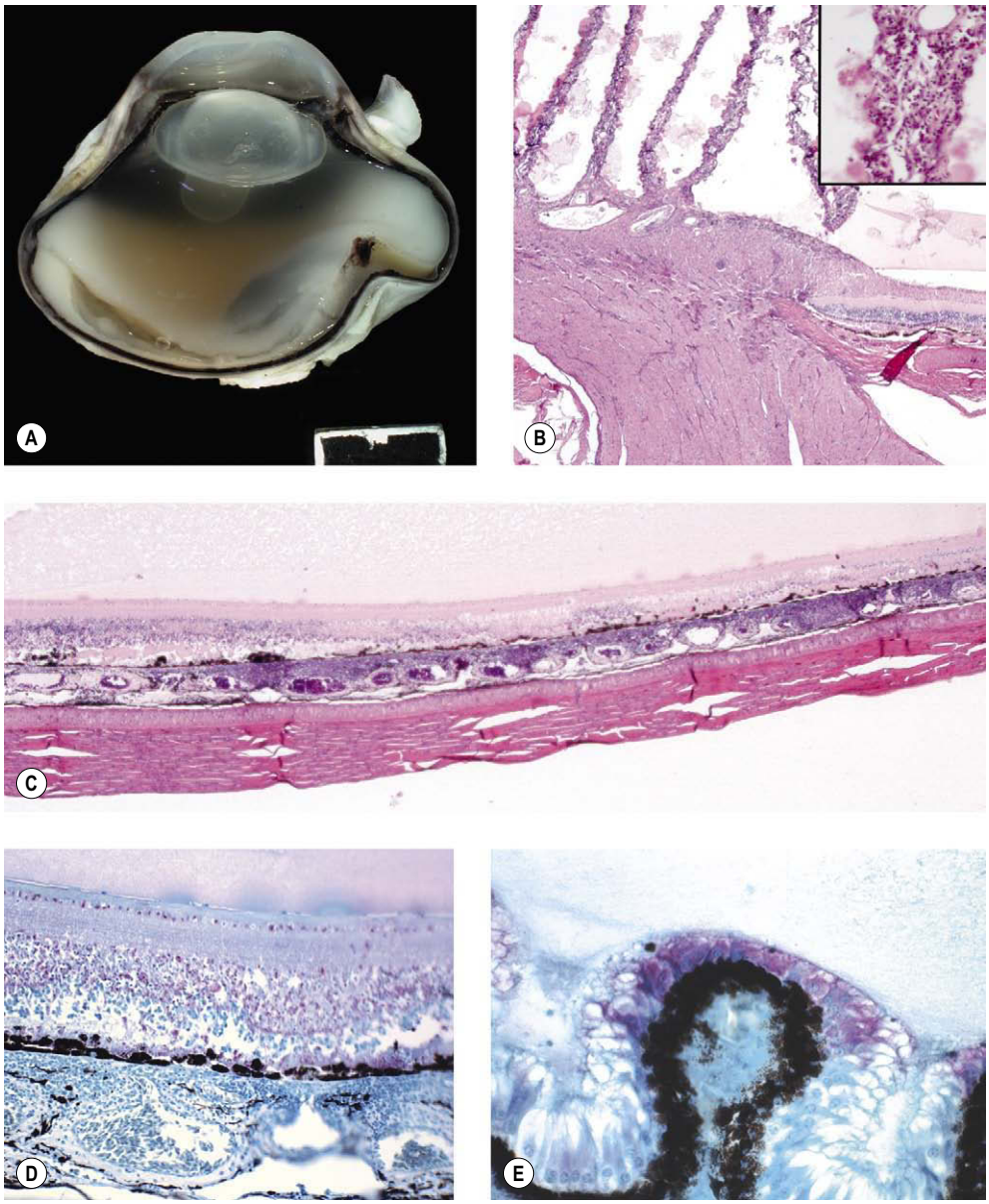


Figure 11.39 West Nile virus chorioretinitis in raptors. (A) Gross photograph of a Red-tailed Hawk eye infected with West Nile virus (WNV) showing protein exudates in the vitreous. (B) Photomicrograph showing lymphocytic infiltrates in the pecten. The inset shows the same with more magnification. (C,D) Immunohistochemistry showing WNV antigen (labeled red) in the retina and in the ciliary body epithelium (D). (E) WNV antigen is in the ciliary body non-pigmented epithelium.

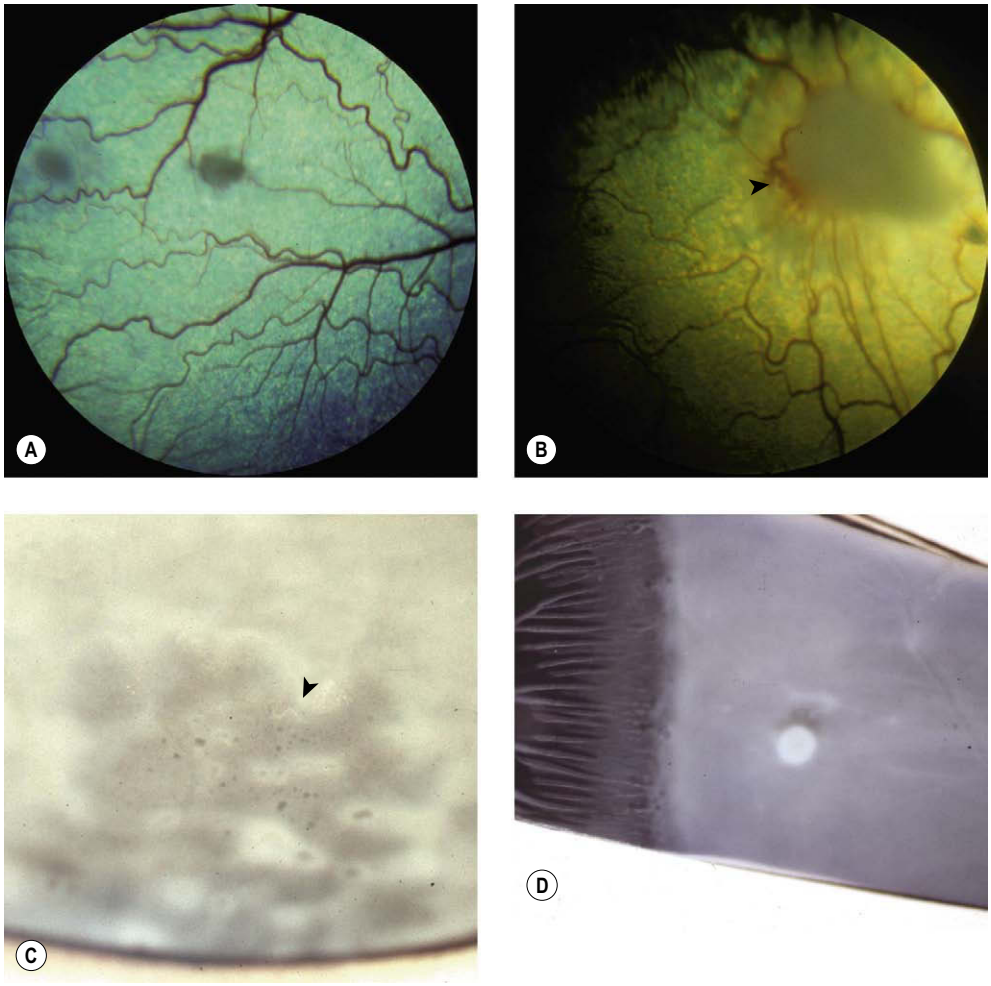


Figure 11.40 *Toxocara canis* ocular larva migrans. (A) Borzoi, 1 year old: two focal granulomas are present in the temporal retina. The diagnosis was based on the dog's age, health and response to treatment. (B) Golden Retriever, 5 months old: this intraretinal granuloma has perilesional edema and neovascularization (arrow). *Toxocara canis* larvae were identified in the eye and the brain of this seizuring dog. (C) Gross photograph of the posterior segment from a young dog showing a migrating larva of *Toxocara canis* (arrow). (D) Gross photograph of the peripheral retina from another young dog showing a discrete granuloma in the retina. It is a good idea to locate and sample these foci to look for larval parasites.

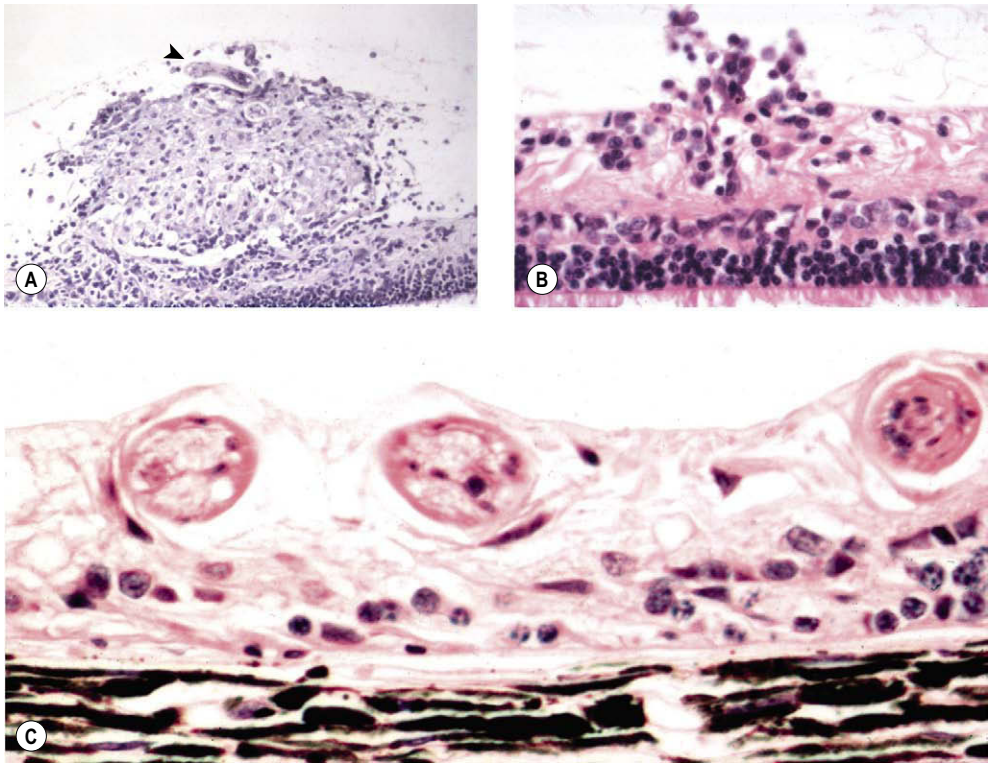


Figure 11.41 *Toxocara canis* ocular larva migrans, histopathology. (A) Photomicrograph showing a section taken from the granuloma in Figure 11.33(D). The section includes a fragment of a larval *T. canis* parasite (arrow). (B) Photomicrograph showing a lymphocytic focus on the inner retina, a feature that should hint at the diagnosis when seen in a young dog. (C) Photomicrograph showing the migrating larva from the posterior segment in Figure 11.33(C).

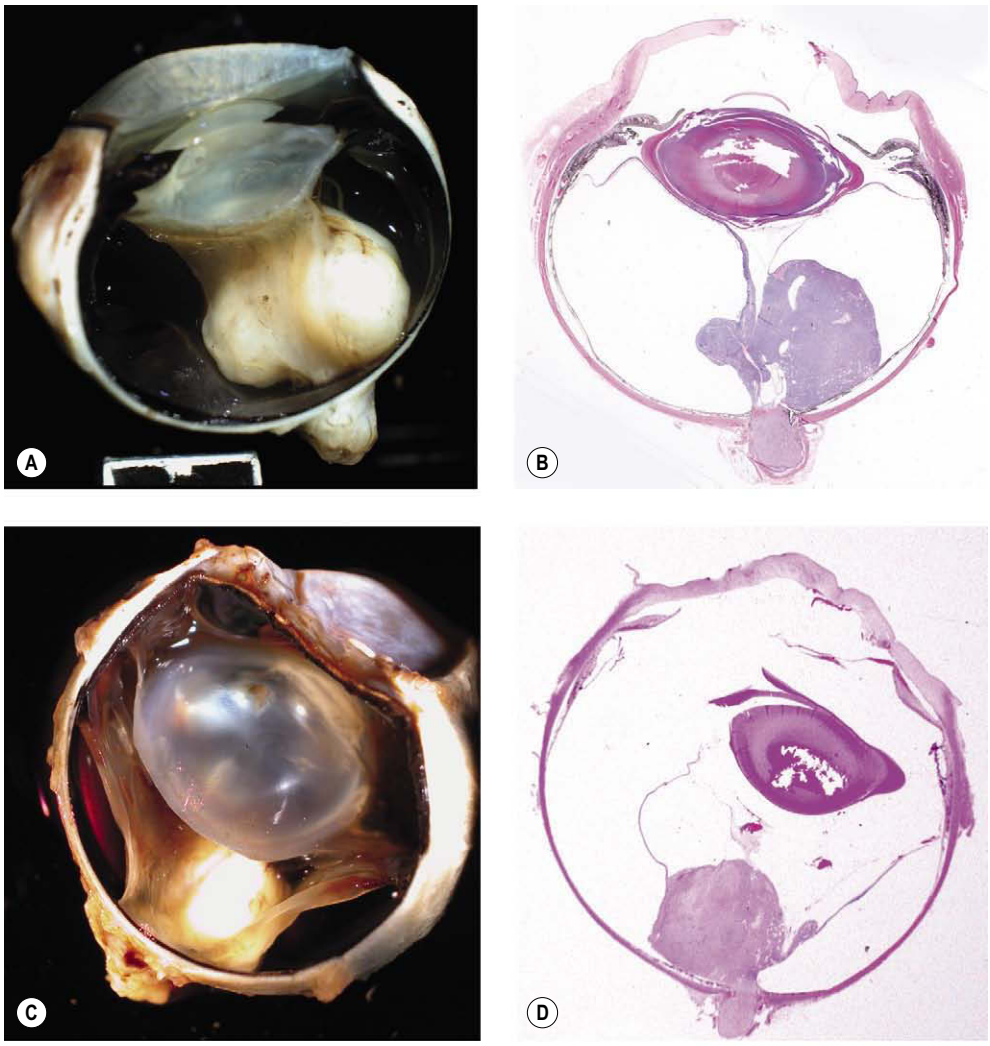


Figure 11.42 Retinal glioma, pathology. (A,B) Gross photograph and subgross photomicrograph showing an astrocytoma in the central retina in a dog. (Reproduced with permission from Naranjo C, Schobert C, Dubielzig RR 2008 Canine ocular gliomas: a retrospective study. Vet Ophthalmol 11:356–362.) (C,D) Gross photograph and subgross photomicrograph of another central retinal astrocytoma in a dog. (E,F) Photomicrographs showing solid tumors within the retina at two different magnifications. The inset in (F) shows glial fibrillary acid protein (GFAP)-positive immunohistochemistry.

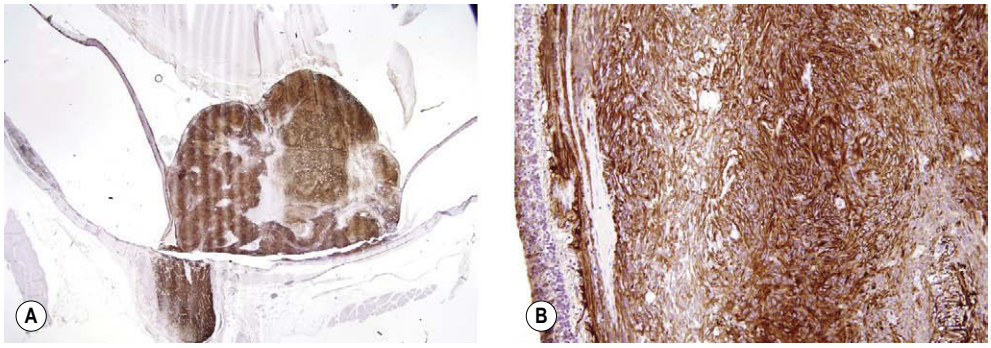


Figure 11.43 GFIP staining in retinal glioma (A,B) Photomicrographs showing positive staining with glial fibrillary acid protein (GFAP).

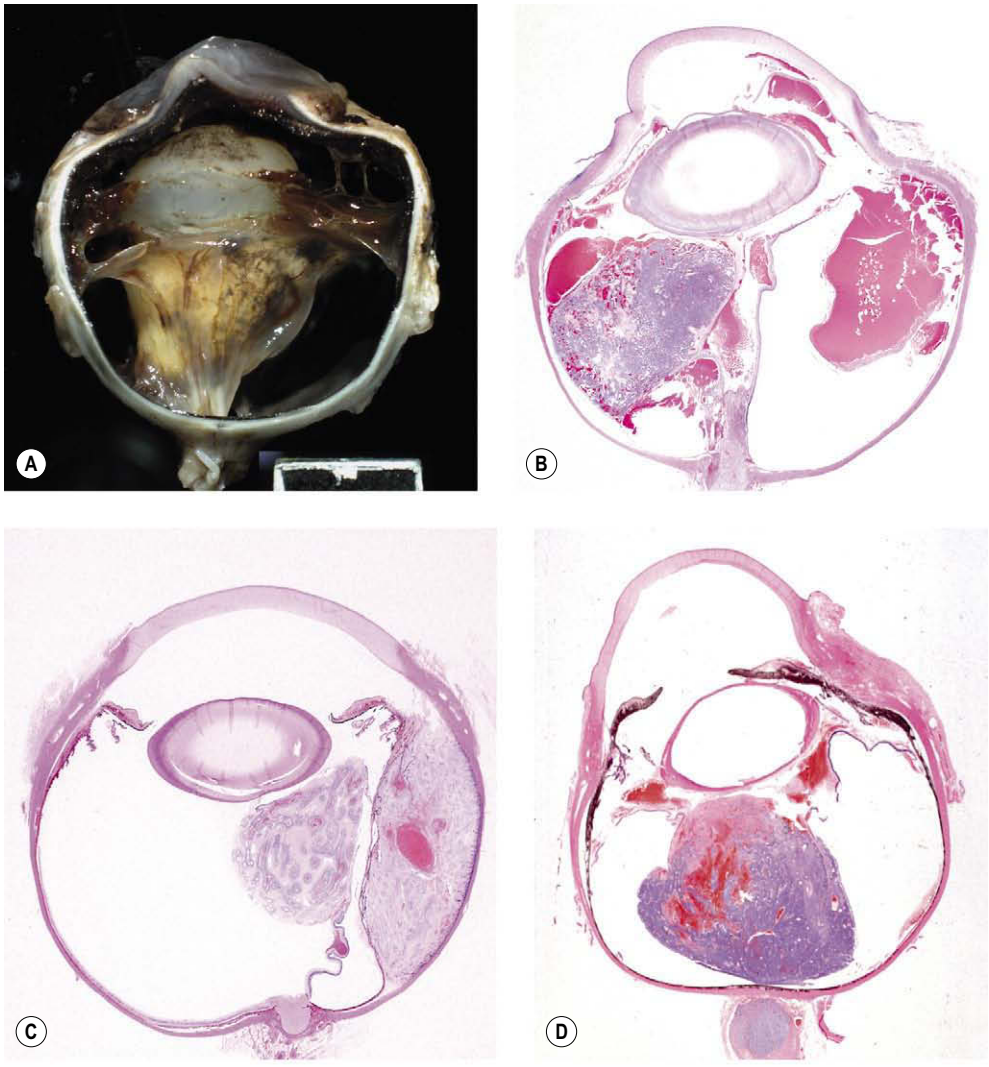


Figure 11.44 Retinal medulloepithelioma and primitive neuroectodermal tumor (PNET). (A) Gross photograph of a canine eye showing a mass within the detached retina. This 5-year-old dog had a retinal tumor composed of primitive neural tissue with cords of epithelium and neuroblastic cells with rosettes. (B–D) Subgross photomicrographs of dog eyes with retinal tumors ranging from primitive to more differentiated tumors: PNET tumor (B), retinocytoma (C) and medulloepithelioma (D). (E) Low magnification of a canine retinal medulloepithelioma showing cords of elongate neural cells in tubular arrays (arrows). (F) Photomicrograph of a Homer–Wright rosette, a feature of any of the varieties of PNET tumors.

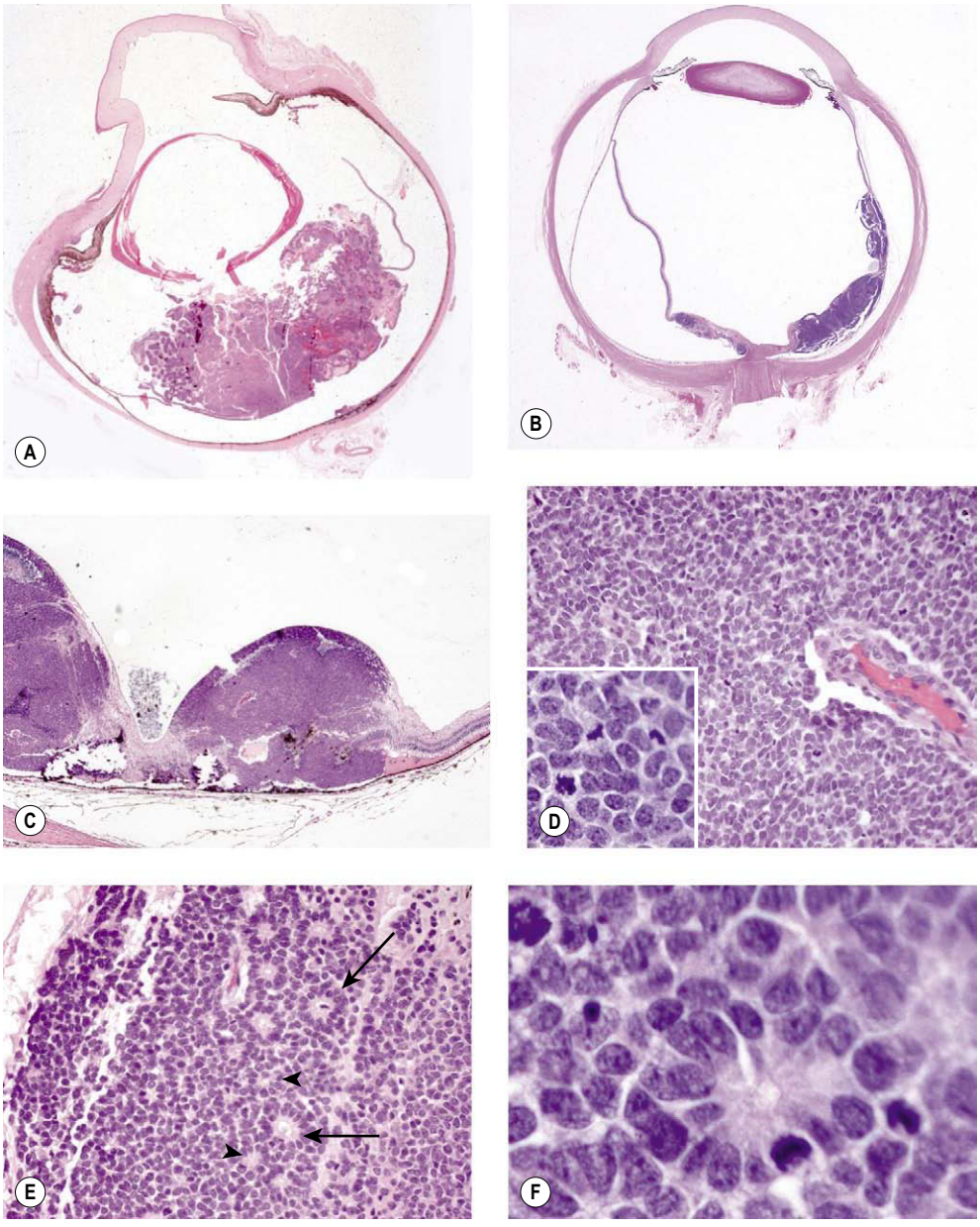


Figure 11.45 Retinoblastoma in humans and animals. (A) Subgross photomicrograph of a retinal tumor from a dog with several features of retinoblastoma, but also some features of medulloepithelioma. (B) Subgross photomicrograph of a human globe with retinoblastoma. (C) Low magnification photomicrograph of human retina with retinoblastoma. (D) Photomicrograph of human retinoblastoma showing typical primitive neural cells in a solid sheet. The inset shows how the darkly staining nuclei tend to mold with one another. (E) Photomicrograph showing Homer–Wright (arrowheads) and Flexner–Wintersteiner rosettes (arrows). (F) Higher magnification photomicrograph showing a Flexner–Wintersteiner rosette.

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Chapter 12

The Optic Nerve

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NORMAL ANATOMY (Fig. 12.1)

Optic nerve head, intraocular optic nerve (optic disc, optic papilla)

- The optic nerve is mostly composed of the axons from the retinal ganglion cells. The retinal ganglion cell axons project centripetally within the nerve fiber layer of the retina, before converging at the optic nerve head and turning posteriorly to project towards the brain
- There is a central depression within the optic nerve head, called the physiologic cup and this area is supported by a thickening of the inner limiting membrane, i.e. processes of native glial cells, called the supporting meniscus of Kuhnt
- Peripheral to these glial cells, blood vessels enter from the orbit and spread out to form the retinal vessels. Unlike primate species, dogs and cats lack a central retinal artery. The canine and feline optic nerve and retina receive their blood supply from the short posterior ciliary arteries, derived from anastomosis of the large external ophthalmic artery and the smaller internal ophthalmic artery
- In dogs, a small dark spot within the center of the optic nerve head is known as the physiologic pit, which is considered a remnant of the hyaloid artery. An exaggeration of the normal thickening of glial cells over the optic nerve is also considered to represent a remnant of the hyaloid artery, and is termed 'Bergmeister's papilla'. More pronounced vascular remnants of the fetal hyaloid artery often persist in cattle, as tubular structures projecting anteriorly from the optic nerve head into the vitreous
- In dogs myelination of retinal ganglion cell axons in the optic nerve begins at the optic chiasm and extends to the optic nerve head, with variable myelination extending within the peripapillary nerve fiber layer, accounting for the very irregular shape of the optic nerve head seen in many dogs
- In cats, myelination stops at the lamina cribrosa and the optic nerve head appears relatively small, dark and round
- In horses, the optic nerve head is typically a horizontally oriented oval with a very well-developed lamina cribrosa structure.

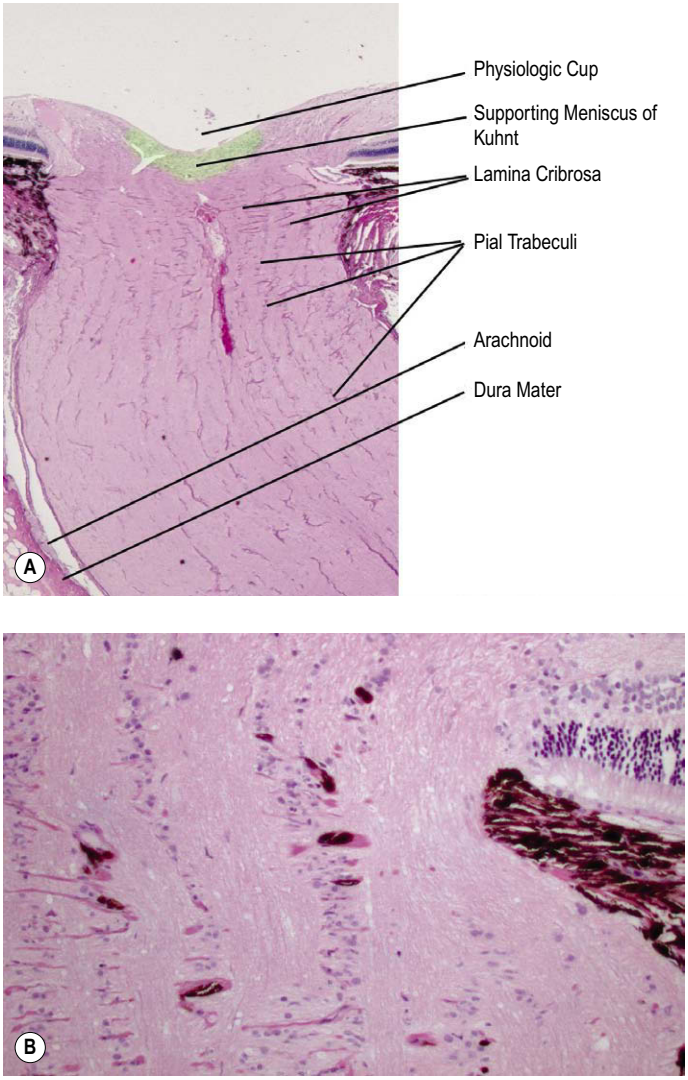


Figure 12.1 Normal optic nerve. (A) Photomicrograph showing the normal morphological features of the canine optic nerve and optic nerve head. (B) Higher magnification photomicrograph showing the optic nerve tissue within the lamina cribrosa.

The intrascleral optic nerve

- The region of the sclera through which bundles of optic nerve axons pass is called the lamina cribrosa. The lamina cribrosa is a structure, consisting of collagenous beams or plates, that spans the optic nerve. This connective tissue meshwork also contains elastin and lends support for the nerve tissue
- In glaucoma, physical distortion resulting from elevation in intraocular pressure leads to outward bowing of the lamina cribrosa and physical distortion and misalignment of the laminar plates, with resulting compression of axons (see Ch. 13).

The intraorbital optic nerve

- The intraorbital optic nerve has an S-shaped bend to accommodate for globe movement within the orbit
- The optic nerve may be considered to represent a white matter tract of the brain and is ensheathed by the meninges
  - Dura mater
    - Collagen-rich layer farthest from the nerve bordering the orbital tissue
    - This tough, outermost dural sheath fuses with the orbital periosteum at the entrance to optic canal (optic foramen) and is also continuous with the lining of the cranial vault
  - Arachnoid mater
    - The arachnoid mater is a highly cellular layer with scant collagen poorly or unattached to the dura mater. The cells of the arachnoid are often large and form epithelial-like clusters which can be very numerous immediately adjacent to the globe
    - The cerebral spinal fluid circulates in the space between the arachnoid and the innermost pia mater
    - Arachnoid cap cells are clusters of epithelial-like cells which extend through the dura mater and form clusters in the soft tissue of the orbit
      - It is from these arachnoid cap cells that canine orbital meningioma arises
  - Pia mater
    - The collagenous and vascular layer closest to the optic nerve and continuous with the pial septae which penetrate the neuropil of the nerve and divide the tissue into columnar subunits.

The intracanalicular optic nerve

- Posterior to the orbit, the nerve enters the bony optic canal.

The intracranial optic nerve

- Represents a small portion of the nerve which merges into the optic chiasm, where a proportion of the axons cross over, or decussate, to the contralateral side before projecting to the lateral geniculate nuclei as the optic tracts
  - The percentage of optic nerve axons that decussate at the optic chiasm ranges from about 50% in the primate, 65% in cats and 75% in dogs, to 100% in avian species.

Comparative Comments

In general, the human optic nerve conforms to the description given earlier for the canine and feline optic nerve. The human optic nerve contains approximately 1 million fibers and is about 5 cm long. A branch of the ophthalmic artery gains access to the nerve through the dura approximately 1 cm posterior to the globe, and pial branches provide the blood supply posteriorly.

CONGENITAL AND HEREDITARY DISEASES

Canine optic nerve hypoplasia (Figs 12.2, 12.3)

There are 15 canine cases of optic nerve hypoplasia in the COPLOW collection, 10 of which are bilateral.

- Although no clear breed predilection is evident in the COPLOW collection, optic nerve hypoplasia is suspected to be inherited in a number of breeds including Dachshunds, Poodles and Shih Tzu

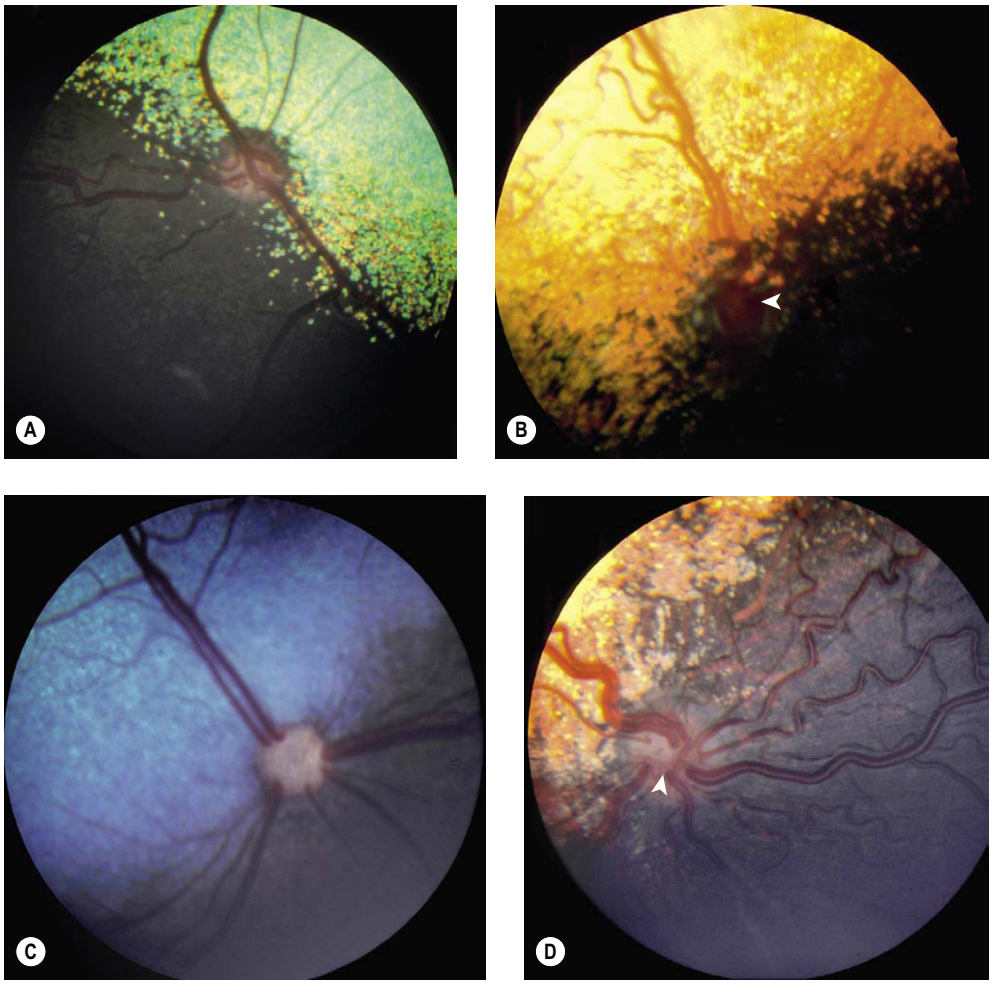


Figure 12.2 Optic nerve hypoplasia, fundus. (A) Lhasa Apso, 8 months old: the small optic disc is slightly depressed. (B) Miniature Poodle, 6 months old: the very small, depressed disc (arrow) is located in the non-tapetal area. (C) Bernese Mountain Dog, 8 weeks old: the optic disc looks cat-like as the retinal vessels drop over the edge of the disc. (D) Collie, 4 months old: the optic disc is poorly discernible (arrow), as the major venules appear to be confluent.

Morphologic features of canine optic nerve hypoplasia

- A small diameter optic nerve head and optic nerve
- The neuropil is densely gliotic
  - This feature can be surprisingly hard to recognize unless one is very familiar with the normal appearance of nerve tissue
- A careful search often reveals vestigial remnants of optic nerve glial tissue in orbital tissues outside the optic nerve proper. The most common place to find these remnants is within peripheral nerve tissue
- The retina always has markedly decreased numbers of ganglion cells and there may be segments of retina with more profound atrophy
- Several cases within our collection have retinal blood vessels which leave the retina itself and extend into the vitreous
  - This change is peripheral and segmental
  - The far peripheral retina beyond the vascular anomaly is avascular.

Canine optic nerve aplasia (Fig. 12.4)

- There are six canine cases in the COPLOW collection, all unilateral
- There is no particular bred predilection

Morphologic features of canine optic nerve aplasia

- No optic nerve tissue is detectable grossly or microscopically, except for the rare appearance of vestigial remnants of glial tissue within peripheral nerve tissue
- The retina is stretched across the back of the lens and makes no contact with the posterior pole of the globe
- The retinal tissue is totally devoid of ganglion cells and there is disorganization of the retinal layers
- The retinal tissue is totally avascular.

Achiasma and congenital nystagmus

- There is a line of black Belgian Sheepdogs with a recessive mutation leading to a chiasmatic optic nerves and congenital nystagmus, that has been studied extensively by vision researchers.

Optic nerve coloboma (Fig. 12.5)

- Colobomas of the optic nerve are rarely submitted to the COPLOW service
- Optic nerve or posterior scleral colobomas can be a part of a more complex syndrome, such as Collie eye anomaly (see Ch. 3) or feline upper eyelid agenesis (see Ch. 7), or they may present as an isolated abnormality

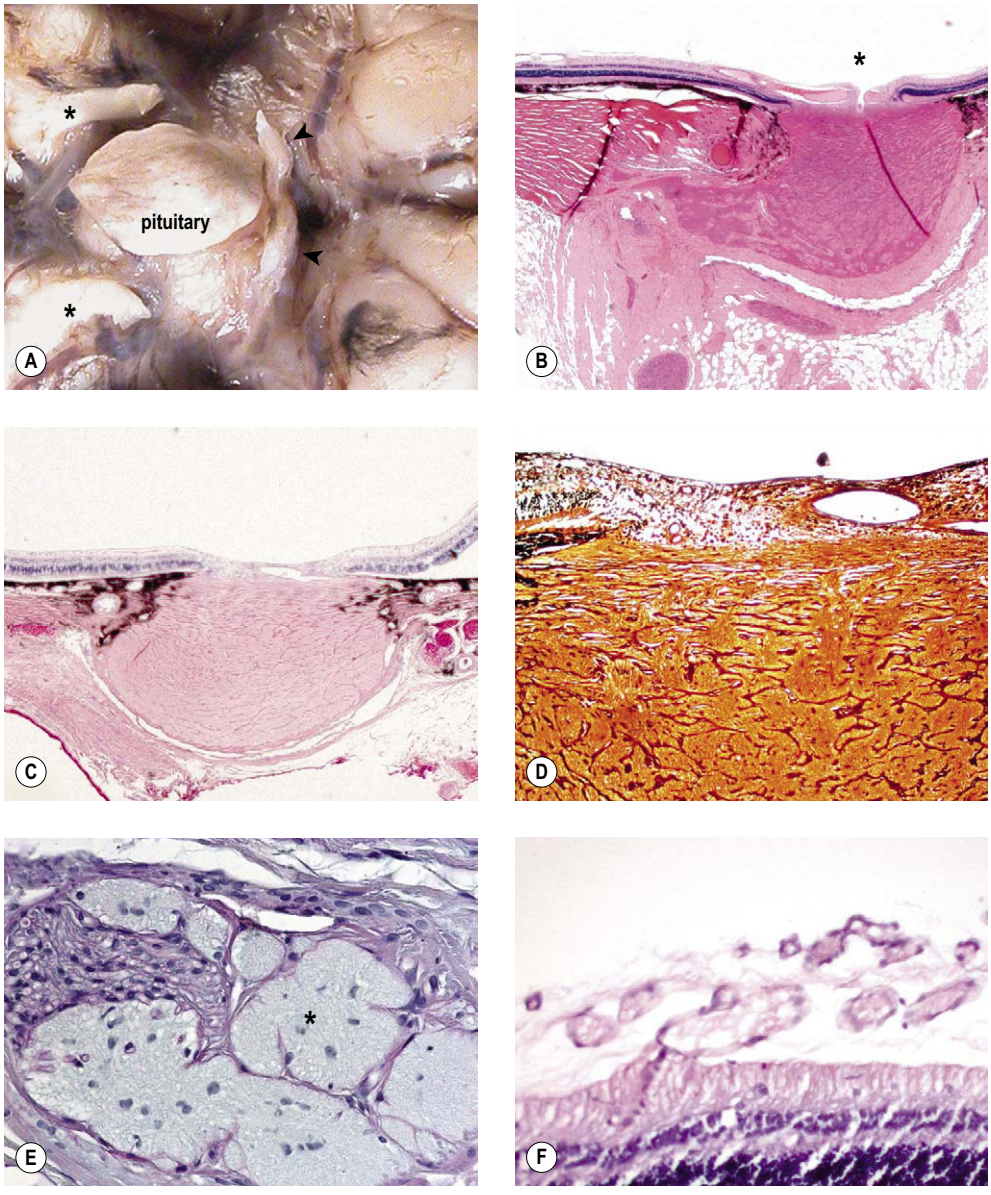


Figure 12.3 Optic nerve hypoplasia, pathology. (A) Gross photograph of the ventral aspect of a dog brain with optic nerve hypoplasia showing vestigial remnants of optic nerve tissue (arrows). (*oculomotor nerves) (B) Low magnification photomicrograph of a canine hypoplastic optic nerve showing a narrow disc (*) and meandering nerve tissue. (C) Low magnification photomicrograph of a young Shih Tzu optic nerve showing hypoplasia. (D) Photomicrograph of the same optic nerve as (C), stained with Bielschowsky silver stain for axons, showing a lack of axons within the neuropil. (E) High magnification photomicrograph of a canine optic nerve showing vestigial remnants of optic nerve neuropil (*) within peripheral nerve tissue. (F) Photomicrograph of the inner retina from an affected dog showing blood vessels extending from the retina into the vitreous. Peripheral to this point the retina becomes avascular.

- There is an inherited predisposition to optic nerve colobomas in Basenji dogs (in which the colobomatous lesions may occur in isolation, or concurrently with persistent pupillary membranes) and in Hereford and Charolais cattle
- Optic nerve head colobomas may be classified according to their location as either 'typical', at the 6 o'clock position in the location of the fetal fissure, or 'atypical' if away from this location

Morphologic features of optic nerve colobomas

- The nerve head is widened and there is an outward bulging of vitreous
- A segmental defect in the lamina cribrosa and ectasia of the posterior sclera.

Comparative Comments

As in the dog and cat, the major congenital anomalies of the optic nerve in humans are hypoplasia, colobomatous defects, and pits of the optic nerve head. Minor congenital anomalies include persistence of the hyaloid system on the disk, projection of vascular loops from the disk, myelination of the nerve fibers extending onto the retina, and pigmentation of the disk.

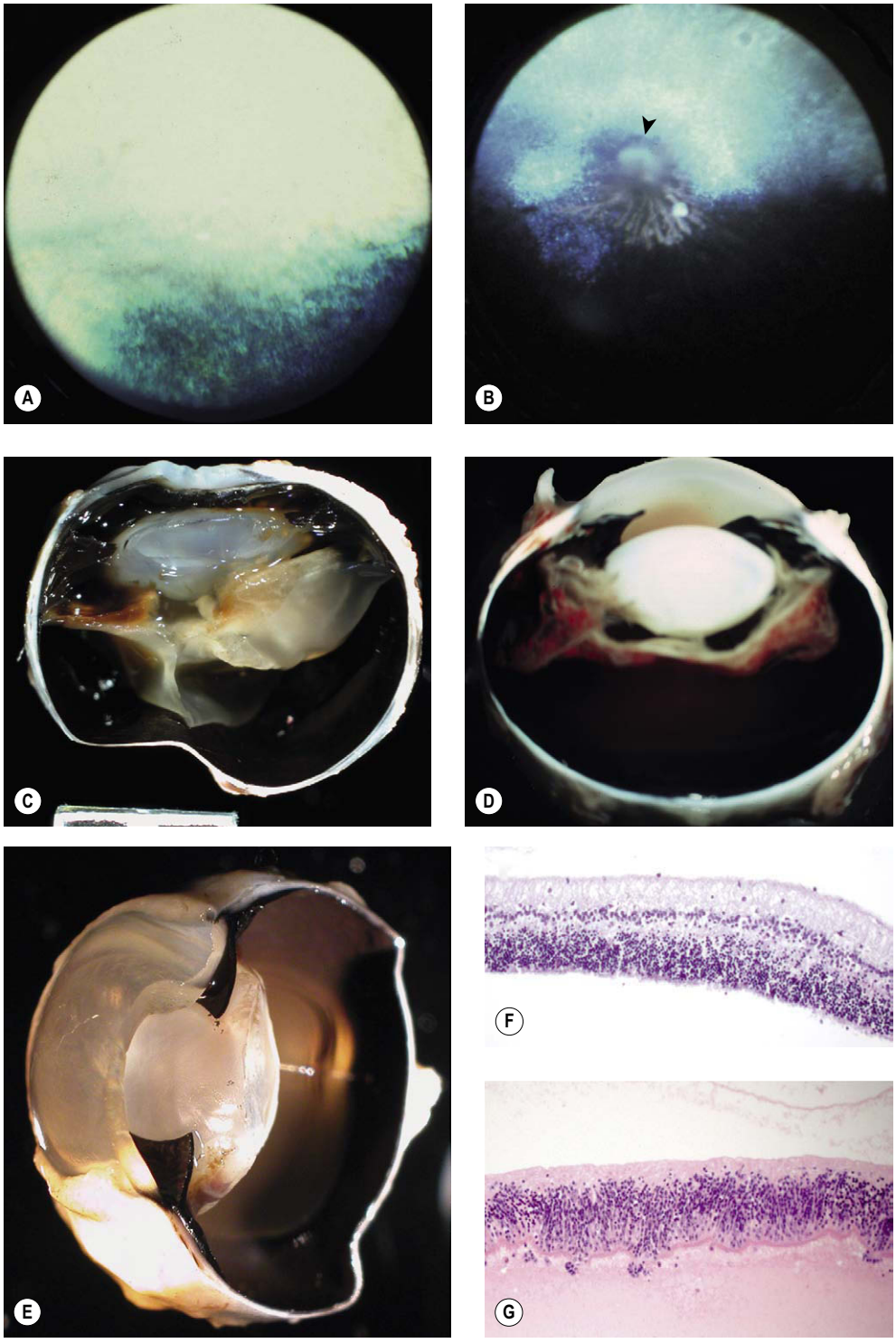


Figure 12.4 Optic nerve aplasia. (A) American Shorthair, 2 months old: only a hyperreflective tapetum is present in the area that should contain the optic disc and retinal vessels. (B) DSH, 9 months old: the tapetum is hyperreflective. White striae are present inferior to a gray amorphous mass (arrow), which supplants the area that should contain the optic disc. (C,D) Gross photographs of canine eyes in which the retina is stretched across the back of the lens and never makes contact with the posterior pole of the globe, because there is no optic nerve. (E) Gross photograph of a dog eye viewed obliquely showing the same feature as (C) and (D). A remnant string of tissue extends to where the optic nerve and optic disc should be. (F,G) Photomicrographs of the retinas from two dogs with optic nerve aplasia showing no ganglion cells or blood vessels.

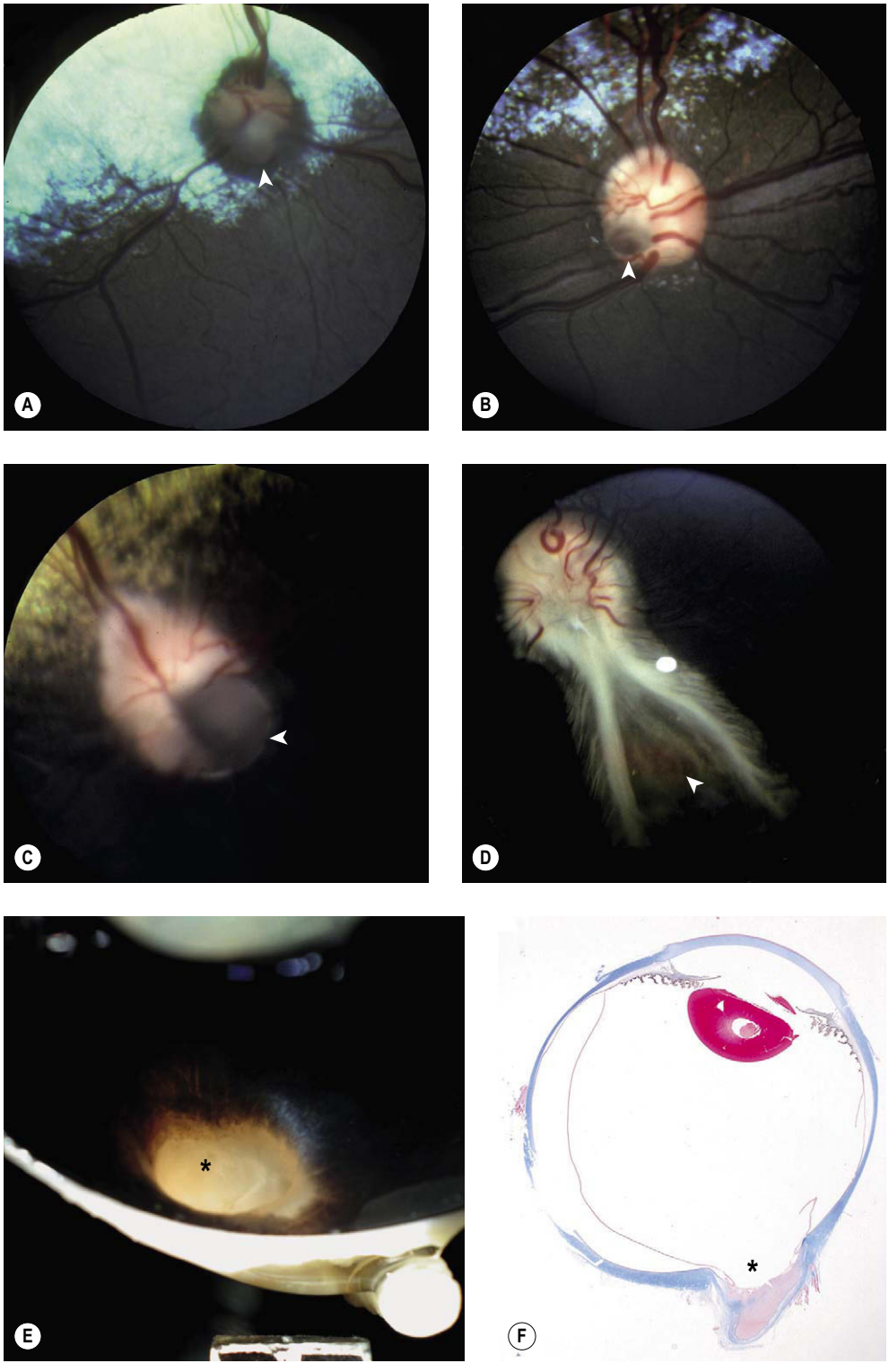


Figure 12.5 Coloboma of the optic nerve head. (A) Basenji, 4 years old: the arrow points to a typical coloboma in the inferior optic disc. (B) Cairn Terrier, 3 years old: a small coloboma is identified by the arrow. (C) Cocker Spaniel, 3 years old: this large coloboma (arrow) involves about a quarter of the optic disc. (D) Great Dane, 1.5 years old: this is the right optic disc in a bilateral condition. The arrow points to a coloboma that extends into the disc. Abnormal myelination extends on both sides of the coloboma. (E) Gross photograph showing an equine optic nerve head coloboma (*). (F) Subgross photomicrograph of the same eye as (E) showing optic nerve head coloboma (*) (trichrome stain).

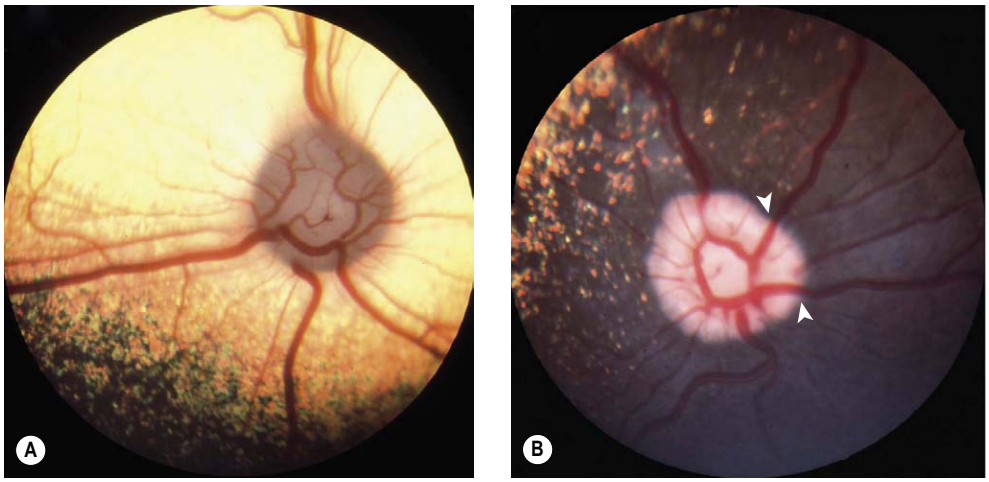


Figure 12.6 Papilledema, clinical. (A) Chinese Crested Powderpuff dog, 2 years old: the optic disc is 'full' and extends vitreal. The borders of the disc are indistinct. Hydrocephalus was diagnosed based on CT scan. (B) Shetland Sheepdog, 4.5 years old: this dog developed severe ataxia. The retinal vessels have a characteristic bend (arrows) as they extend over the edge of the elevated disc.

OPTIC NERVE SWELLING, TRAUMA AND DEGENERATION

Papilledema (optic disc swelling, edema) (Fig. 12.6)

- Increased pressure in the calvarium or central nervous system for any reason can result in clinically apparent swelling and anterior displacement of the optic nerve head known as papilledema
  - Papilledema may be recognized in association with CNS neoplasia, hydrocephalus, orbital masses and calvarial hyperostosis, causing direct compression of the optic nerve or increased CSF pressure
  - Papilledema may be associated with variable visual and pupillary light reflex deficits
  - Papilledema in dogs may be difficult to recognize clinically, due to the high degree of variation in the presence of myelination of canine optic nerve heads
- Globes with documented papilledema are seldom brought to the attention of a pathologist when the globe is available at necropsy. There are no examples of papilledema in the COPLOW collection.

Papilledema and optic nerve degeneration in Vitamin A deficient in cattle

The COPLOW collection contains a small series of cases of vitamin A deficient optic neuropathy in a one small group of cattle.

- Vitamin A deficiency optic neuropathy is well-documented in the veterinary literature
- In addition to causing night-blindness and progressive retinal degeneration in adult cattle, vitamin A deficiency in calves and young, growing cattle, is associated with papilledema and optic nerve degeneration
- Narrowing of the optic canals, due to excess bone deposition, thickening of the dura and increased CSF pressure all contribute to compression, edema and ischemia of the optic nerves
- Malacia and demyelination of the optic nerve axons is associated with blindness and widely dilated pupils.

Glaucomatous optic neuropathy

- Initial swelling of the optic nerve head often precedes optic nerve degeneration in acute glaucoma, particularly in dogs
- Glaucomatous optic neuropathy is considered in detail in Chapter 13.

Optic nerve trauma and malacia in horses (Fig. 12.7)

- This condition is often preceded by a dramatic traumatic event, most commonly a backward fall and head trauma followed by vision loss
  - If the traumatic event is not witnessed, or vision loss is not immediately noticed at the time of optic nerve damage, it may be hard to establish the relationship between the optic nerve lesion and the traumatic event
- Morphologic features of equine optic nerve trauma and malacia
  - There will be total or segmental necrosis followed, very rapidly by gitter cells
  - Gitter cells from the damaged nerve tissue migrate into the vitreous and are seen as white nodules/excrescences protruding anteriorly into the vitreous from the optic nerve head (exudative optic neuropathy)
    - The clinical appearance of pale extrusions of optic nerve material into the vitreous is considered a poor prognostic indicator for recovery of vision after a traumatic event
  - The end-stage optic nerve lesion involves profound atrophy and fibrosis of the neuropil (Fig. 12.8)
- The syndrome of optic nerve trauma in horses results in an end-stage appearance that is very similar to optic nerve ischemia and only the history can distinguish between the two
  - Profound optic nerve atrophy with peri-papillary retinal degeneration has been reported in horses following episodes of profuse hemorrhage, and following surgical occlusion of the external and internal carotid and greater palatine arteries.

Comparative Comments

Vascular optic neuropathy is an important entity in human ophthalmology. This disorder can be divided into prelaminar, paralaminar, and retrolaminar vascular disease, depending on the site of ischemia.

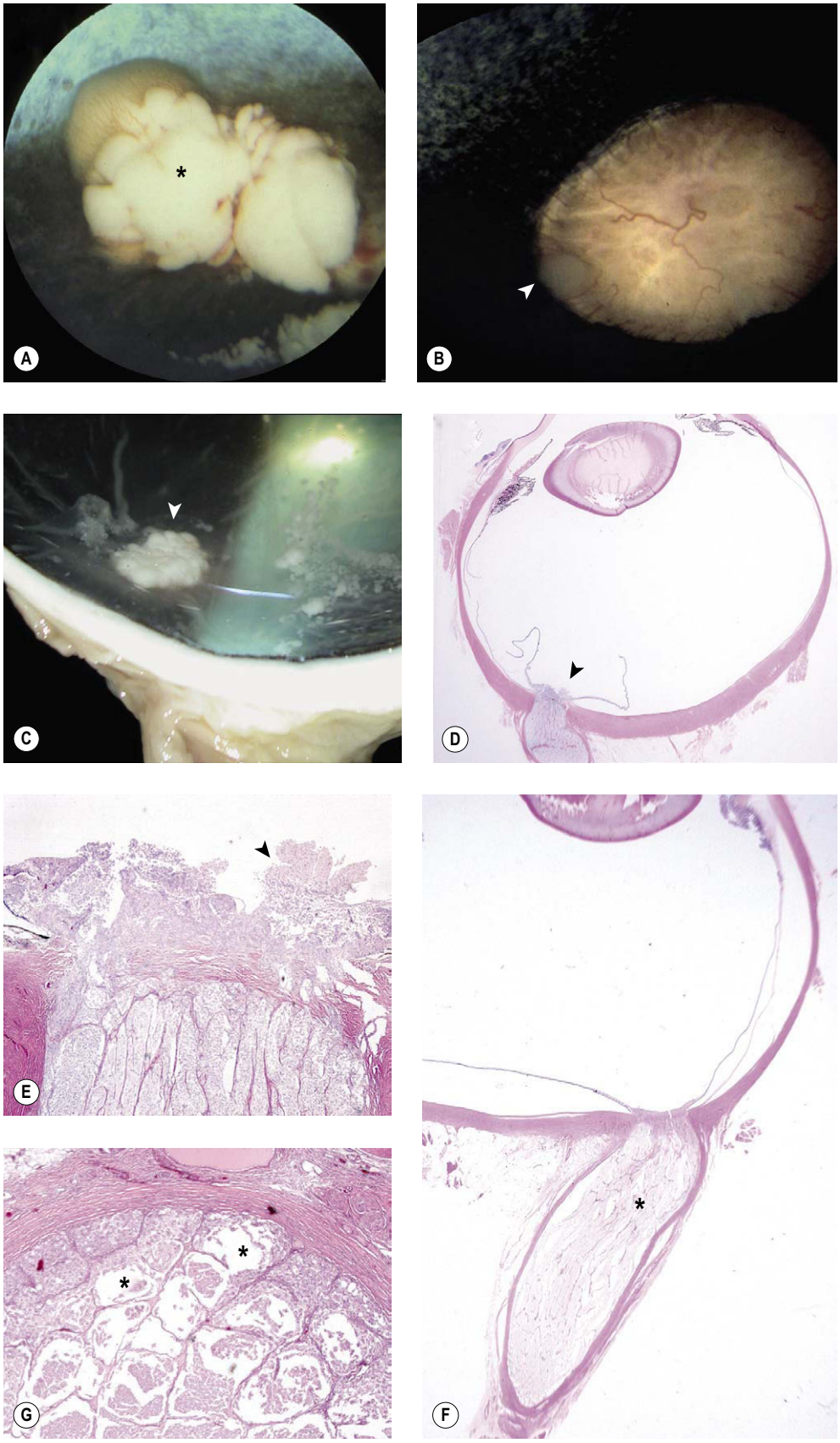


Figure 12.7 Equine traumatic optic neuropathy (equine optic neuritis/neuropathy) (A) Fundus photograph of an equine eye showing a plume of necrotic nerve tissue extruding into the vitreous from the disc (*). (B) Fundus photograph showing a similar disc to (A), but less affected (arrow). (C) Gross photograph of an equine globe showing similar extrusion of necrotic nerve tissue in optic nerve malacia (arrow). (D) Subgross photomicrograph of an affected equine globe showing similar extrusion of necrotic material from the disc (arrow). (E) Higher magnification of the disc from (D). The extruded material (arrow) is a combination of granular necrotic neuropil and macrophage cells (gitter cells). (F) Subgross of another equine globe showing a swollen and pale necrotic optic nerve (*). (G) Cross-section from the same nerve as (F) showing cavitations within the nerve tissue (*) filled with protein-rich remnants.

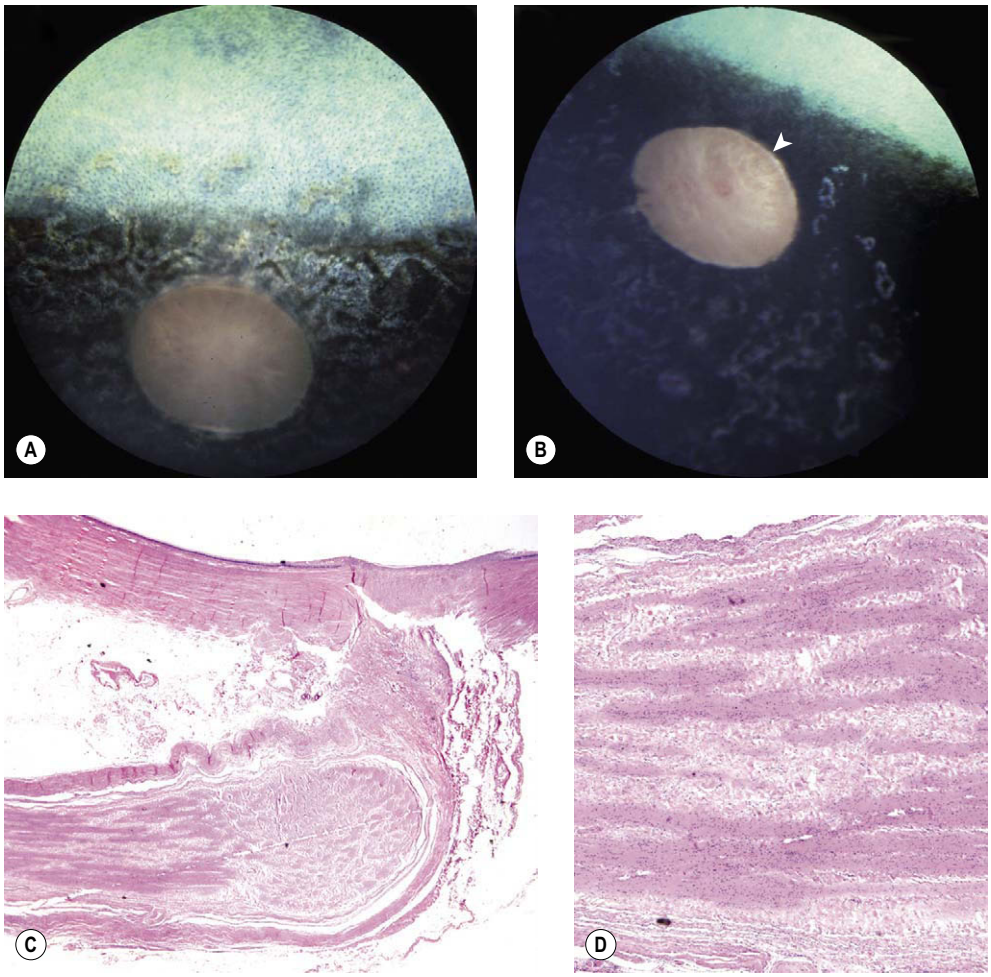


Figure 12.8 Equine traumatic or ischemic optic neuropathy, end-stage optic nerve fibrosis. (A) Thoroughbred, 6 years old: the optic disc is totally atrophic and devoid of vessels. The peripapillary depigmentation indicates retinal atrophy. This stallion was previously kicked in the head. (B) Thoroughbred, 4 years old: the optic disc is atrophied. Attenuated vessels were still present superiorly (arrow). The pigment changes seen in the non-tapetal retina indicate retinal atrophy. This horse had been struck by lightning. (C,D) Photomicrographs of atrophy and fibrosis developing in the optic nerve of a horse, following traumatic optic nerve necrosis.

Optic nerve trauma and proptosis in dogs and cats (Figs 12.9, 12.10)

In 43 of the 80 canine globes in the COPLOW collection with a history of proptosis, there is optic nerve necrosis, malacia, fibrosis, or gliosis depending on the time between the proptosis and enucleation (see Ch. 5)

- There are only two feline globes enucleated after proptosis in the collection and both have optic nerve necrosis
  - Traumatic proptosis is much less common in cats and dolichocephalic dogs than in brachycephalic dogs, and when it does occur it is generally accompanied by severe damage to ocular and optic nerve tissues as well as other signs of significant head trauma
- The most common finding is global necrosis of the optic nerve, commencing immediately, at the time of proptosis
  - This could be due to ischemia, or crushing of the nerve tissue because of stretching and a drawing together of the dura mater
- Optic nerve trauma can also occur in the absence of globe proptosis, or in proptosed globes that are replaced surgically, and these are unlikely to be removed, or at least are unlikely to be examined by a pathologist. However, the clinical consequences are similar (Fig. 12.10)
- Trauma to the optic chiasm leading to contralateral blindness has been associated with excessive traction during enucleation procedures in the cat.

Comparative Comments

Human eyes with papilledema are frequently seen in the ocular pathology laboratory, particularly following autopsies.

- Papilledema denotes a swollen disk and is classically associated with an increase in intracranial pressure
  - This leads to distension of the meningeal spaces about the nerve and compression of the nerve itself
  - This constriction results in venous congestion, with leakage of serum into the nerve head, and impedance of axoplasmic flow anterior to the lamina cribrosa
  - The swollen nerve head protrudes into the vitreous cavity and displaces the retina.

Physical injuries to the human optic nerve may be divided into:

- Orbital injuries, which produce proptosis and avulsion of the optic nerve
- Skull injuries, with fractures in the area of the optic foramen.

The pathologic picture of avulsion of the optic nerve shows extensive exudate and hemorrhage. Fractures or contusions in the area of the optic foramen are commonly seen and result in optic atrophy and blindness. Non-accidental injuries in infants (the shaken baby syndrome) may be followed by subdural and subarachnoid hemorrhage around the optic nerve, papilledema, and if the infant survives, optic atrophy. In addition, a variety of chemical injuries and radiation injuries can occur, which also may lead to optic atrophy.

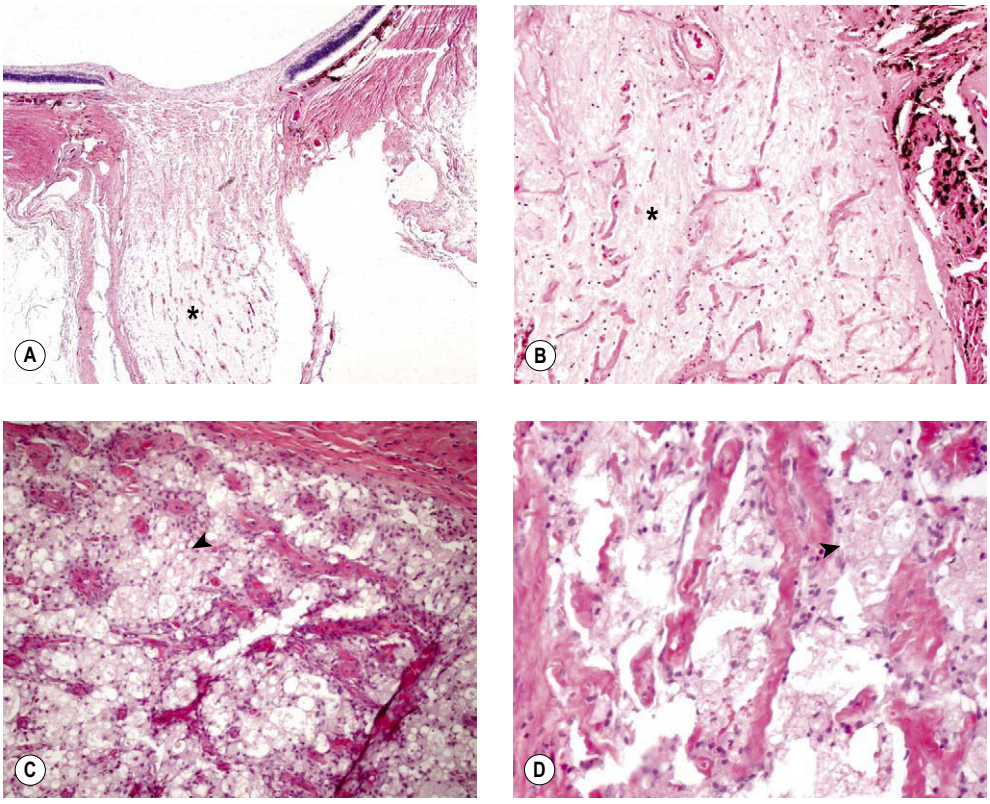


Figure 12.9 Optic nerve necrosis in traumatic proptosis. (A) Low magnification photomicrograph of a canine optic nerve showing global necrosis (*) after proptosis. (B) Higher magnification of another canine optic nerve after proptosis, where the eye was removed 2 days after the traumatic event. There is global necrosis (*) and loss of tissue detail, but not yet phagocytosis. (C) Gitter cells (arrow) consume the necrotic neuropil of an affected canine optic nerve in an eye removed 7 days after trauma. (D) Atrophy and collapse of remnant nerve tissue after the gitter cells (arrow) begin to recede.

INFLAMMATION OF THE OPTIC NERVE (Figs 12.11, 12.12)

Inflammation of the optic nerve is seen quite frequently in clinical practice, often as a part of more generalized inflammatory processes involving the CNS, orbit or eye.

Clinical findings indicative of optic neuritis include

- Swelling and vascular congestion of the optic nerve head
- Indistinct margins of the optic nerve head and peripapillary retinal edema and/or exudates
- Detachment of the peripapillary retina
- Hemorrhages within the retina or on the surface of the optic nerve head
- Reduced vision with afferent pupillary light reflex deficits
- Inflammation that is confined to the retrobulbar optic nerve may result only in reduced or absent vision and altered pupillary light reflexes, in the absence of ophthalmoscopic abnormalities.

Specific inflammatory conditions primarily affecting the optic nerve are comparatively rarely encountered in a pathology service. In the absence of other signs of CNS, orbital or intraocular disease, idiopathic/presumed immune-mediated optic neuritis is unlikely to warrant either enucleation or euthanasia. In the COPLOW collection there are single cases of the following conditions:

Granulomatous meningoencephalitis (GME)

- Optic nerve involvement may occur in isolation, precede or occur in association with other, multifocal CNS lesions and associated clinical signs. Canine GME is a relatively common, and probably under-diagnosed, cause of both optic neuritis and of central blindness in dogs
- Definitive ante mortem diagnosis can be difficult, although elevated CSF protein with pleocytosis, and CT or MRI findings may be considered suggestive of GME
- Small dog breeds and females appear to be predisposed
- Longer survival times appear to be associated with focal GME, such as optic neuritis, than with the multifocal form
- Immunosuppressive therapy may restore vision in affected dogs, but a relapsing-remitting course is common despite therapy

Morphologic features include:

- Histiocytic cells forming cuffs around blood vessels and featuring reticulin fibers around individual histiocytic cells

The pathogenesis of this condition is unknown

Canine distemper optic neuritis

- The disease is associated with infection by Canine distemper virus (paramyxovirus)
- Optic neuritis may occur in isolation or be recognized before, concurrently, or after other systemic signs, such as respiratory, gastrointestinal or neurological, or signs of ocular disease, such as keratoconjunctivitis or retinochoroiditis
- Morphologic features include:
  - Astrocytosis
  - Loss of myelin
  - Eosinophilic intranuclear inclusion bodies

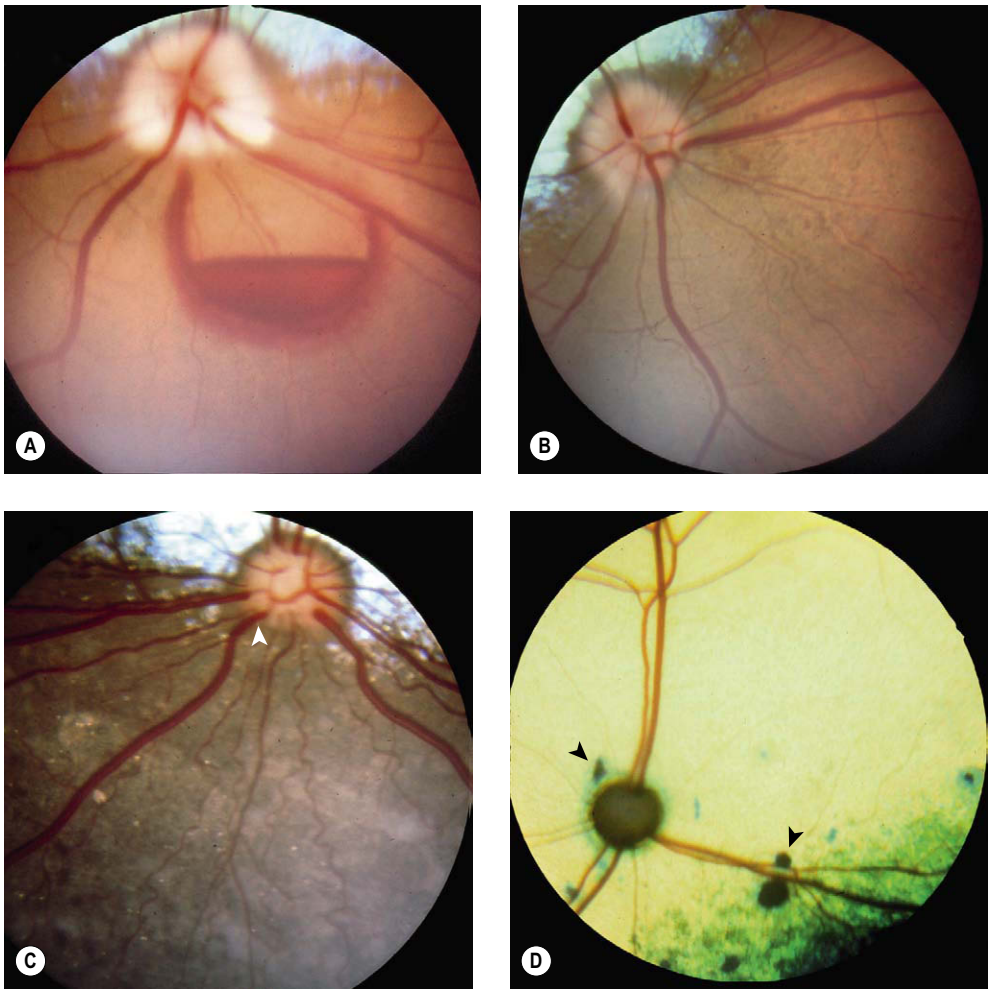


Figure 12.10 Optic nerve trauma, funduscopy. (A) Doberman Pinscher, 3.5 years old: this dog was hit in the eye with a blunt instrument 2 weeks prior to the photograph. The optic disc is swollen and preretinal hemorrhage is present. (B) This is the same dog as in (A), 14 weeks later. The optic disc is atrophic and has demyelinated. (C) Mixed Breed, 6.5 years old: the dog was hit by a car 3 months prior to the photograph. The optic disc is pale and indistinct. The retinal vessels can be seen dropping over the edge of the depressed disc (arrow). (D) DSH, 10 years old: this left eye became blind following enucleation of the right eye. The optic disc is pale. Abnormal tapetal pigment is also present (arrows).

Feline toxoplasmosis optic neuritis

- Despite the frequent reference to toxoplasmosis in the literature, there is only one case in the COPLOW collection in which toxoplasma organisms were identified
- Morphologic features include hemorrhage, malacia, and finding the organism bradyzoites
- The one affected cat had unilateral disease and eventually developed neurologic symptoms
- In veterinary patients, ocular toxoplasmosis appears to be more frequently associated with iridocyclitis and/or chorioretinitis. (Ocular toxoplasmosis is discussed in greater detail in Chapter 9).

Comparative Comments

- Because of the optic nerve's proximity and vascular continuity with the globe and the brain, optic nerve inflammation in the human is most often the result of extension from primary intraocular or intracranial inflammation
- Multiple sclerosis, sarcoidosis, a multisystem granulomatous disease, and Behçet's disease, a multisystem vasculitis, can affect the optic nerve
- A variety of bacterial, viral, and fungal infections can involve the optic nerve and retina (neuroretinitis). Of these, *Varicella zoster-virus*, Mucormycosis, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Toxoplasma gondii* and *Histoplasma capsulatum* are the most important.

TUMORS OF THE OPTIC NERVE

Meningioma

- Canine orbital meningioma (see Ch. 6 for more detailed discussion) (Figs 12.13, 12.14)
  - This is the most common variant involving the optic nerve
    - There are 60 cases of canine orbital meningioma in the COPLOW collection, representing 1.5% of canine tumors in the collection
- Although the tumor originates from the arachnoid cap cells of the optic nerve, the tumor need not be anatomically located within the optic nerve meninges. However, the tumor always extends into the orbital connective tissues encircling the optic nerve

Morphologic features of canine orbital meningioma

- Aggregates of large polygonal cells infiltrating orbital adipose tissue

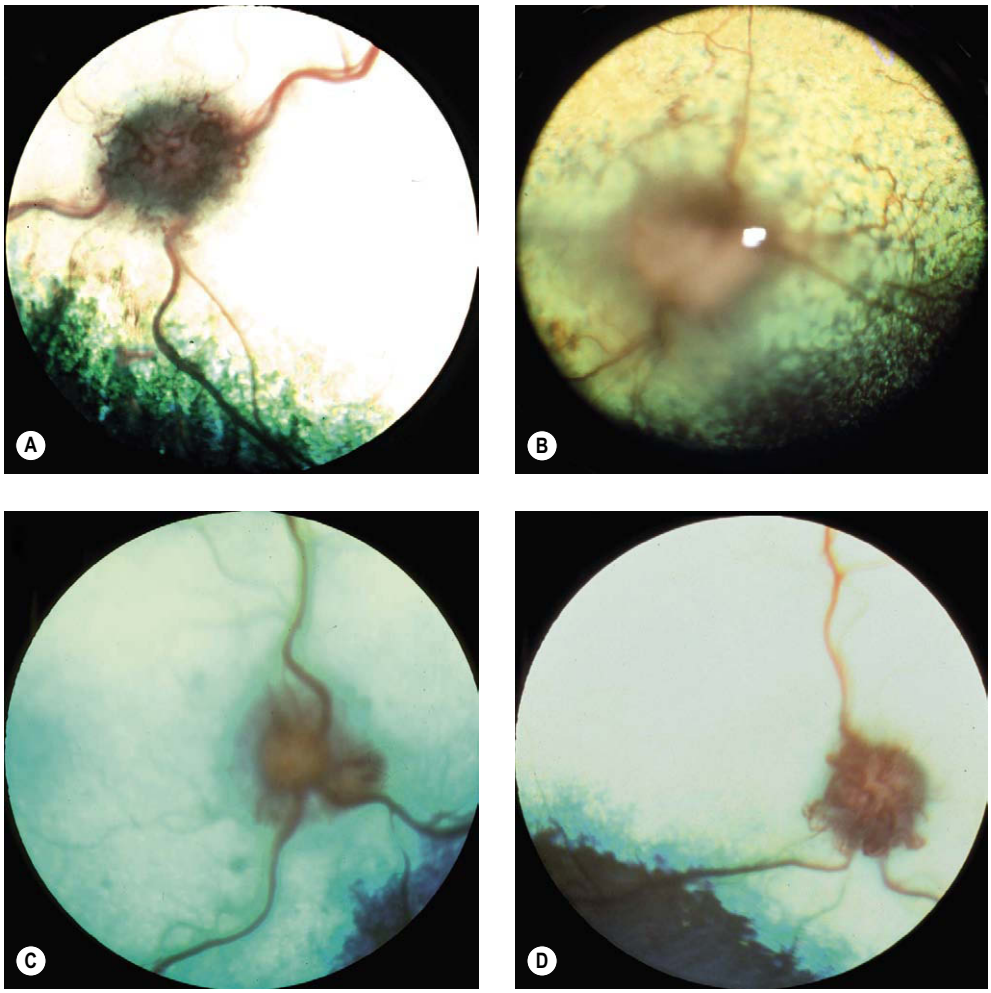


Figure 12.11 Optic neuritis or neoplasia masquerading as neuritis, feline. (A) DSH cat, 2 years old: this blind cat had bilateral neovascularization of the optic disc and peripapillary edema and vascularization. A cerebrospinal tap confirmed lymphosarcoma. (B) DSH cat, 10 years old: a proliferative mass obscures the optic disc. The tapetal retina shows multiple foci of inflammation. Lymphosarcoma was diagnosed on histopathology. (C) DSH cat, 2 years old: the swollen disc, peripapillary edema, infiltrate, and hemorrhage are the most significant lesions. *Cryptococcosis* was diagnosed from a cerebrospinal tap. (D) DSH cat, 8 years old: bilateral neovascularization of the optic disc was the only lesion found in this seizuring cat. Meningioma was the histopathologic diagnosis.

- The cells can be hard to distinguish from epithelial cells but they are vimentin positive and cytokeratin negative
- There are often multiple foci of metaplastic bone, cartilage, or undifferentiated myxomatous stroma

Canine optic nerve meningioma by extension (Fig. 12.15)

- Within the COPLOW collection, there are five canine cases of meningioma with optic nerve involvement by extension from the cranial vault down the optic nerve
- The neoplasm spreads into the optic nerve by extension from the calvarium
- The tumor is limited within the confines of the dura mater, expanding the optic nerve thickness diffusely
- Optic nerve involvement is often bilateral

Morphologic features of canine optic nerve meningioma by extension include:

- The neoplastic tissue expands within the dura mater causing compression of the optic nerve
- Any of the morphologic subtypes that occur in the calvarium can be seen within the optic nerve meninges

In addition to optic nerve meningioma in dogs and humans, there are sparse reports of optic nerve meningioma occurring in other species, including cattle and rats.

Optic nerve glioma (astrocytoma) (Figs 12.16, 12.17)

In the COPLOW collection, this disease is only represented in dogs

- It is unilateral and causes expansion of the optic nerve
- In all 11 cases in the COPLOW collection, the tumor lies near the globe and causes an inward bulging of the optic nerve head
- The tumor can also occur in the central retina and not involve the optic nerve (see Ch. 11), and extensive involvement of the optic chiasm has also been reported

Morphologic features of optic nerve glioma in dogs include:

- There is effacement of the optic nerve neuropil by spindle to stellate neoplastic cells
- The cytoplasmic processes of these cells form a tangle of fibrillar tissue

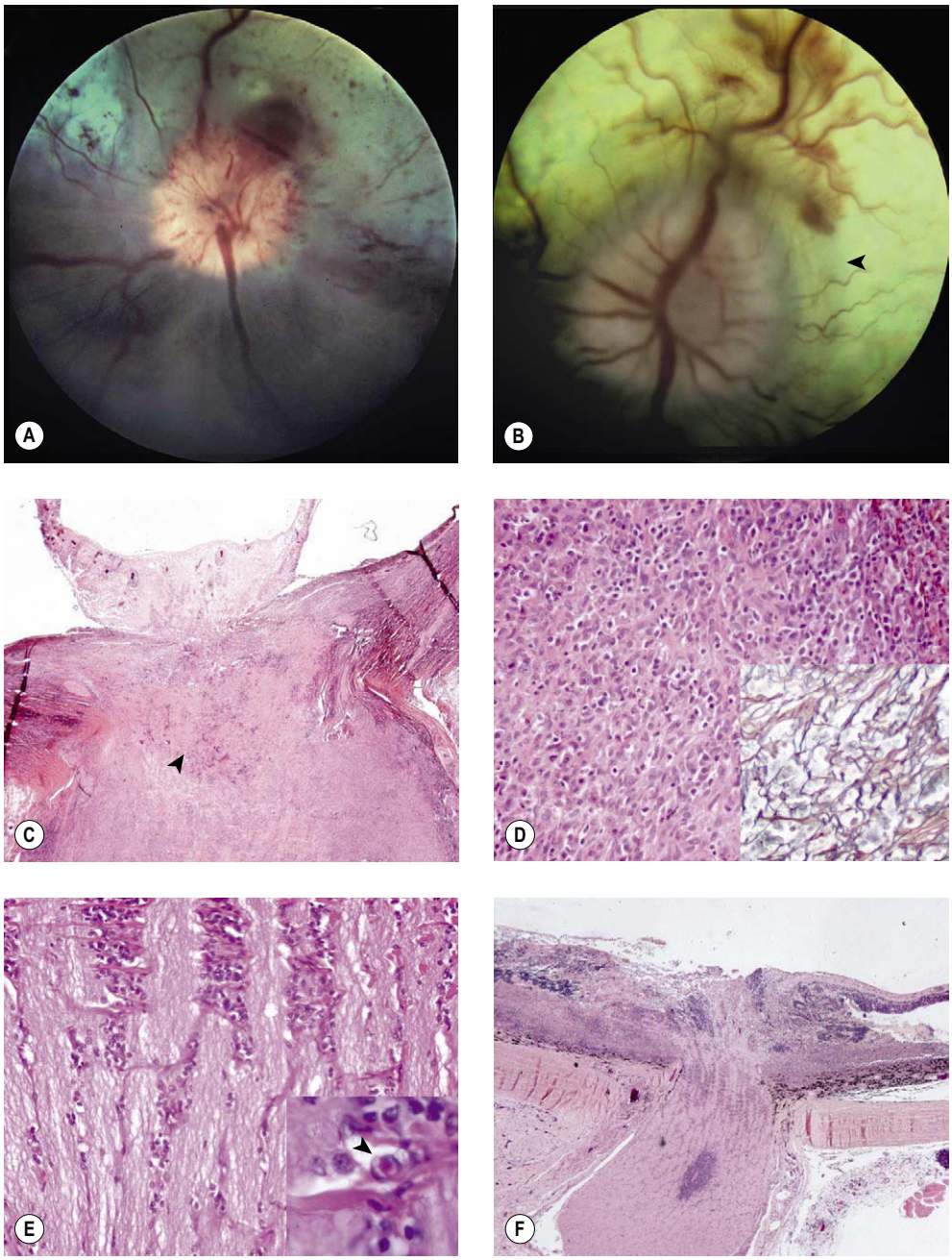


Figure 12.12 Optic neuritis. (A) German Shepherd Dog, 3 years old: the optic disc is severely inflamed with increased vascularization. The peripapillary retina is detached with intraretinal hemorrhage. Granulomatous meningoencephalitis was diagnosed on a cerebrospinal fluid tap from this seizuring dog. (B) Golden Retriever, 4 years old: the optic disc is severely swollen. The peripapillary retina (arrow) is elevated. Intraretinal hemorrhage is also present. Diagnostic work-up and response to therapy were indicative of an immune-mediated disease. (C) Low magnification photomicrograph showing a dog retina and optic nerve with lesions suggestive of granulomatous meningoencephalitis (arrow). (D) Higher magnification of the slide in (C) showing a histiocytic focus. The inset is of a reticulum stain showing the characteristic deposition of reticulum fibers around macrophage cells. (E) Canine optic nerve with gliosis, demyelination and, in the inset, an intranuclear inclusion body typical of canine distemper virus (arrow). (F) Low magnification photomicrograph of a feline eye with extensive inflammatory disease involving the optic nerve, retina, and choroid due to toxoplasmosis.

- The finding of tight, glomerular-like neovascular tangles within the tumor, or in the surrounding retina, can assist with the diagnosis
- Malignant forms with anaplastic cellular features are seen commonly. Cases that extend to the margins of the surgical resection in a biopsy specimen will often re-present with neurologic signs
- The tumor cells are positively labeled for glial fibrillary acidic protein (GFAP) on immunohistochemistry
- Classification system for gliomas/astrocytomas in dogs, from most to least differentiated forms:
  - Astrocytoma
  - Anaplastic astrocytoma
  - Glioblastoma multiforme – considered most aggressive form.

Medulloepithelioma of the optic nerve head in horses (Fig. 12.18)

There is one case in the COPLOW collection

- Medulloepithelioma in the optic nerve head of young horses is very rare
- This is a mass which bulges anteriorly from the optic nerve head and also expands the optic nerve tissue. Exophthalmos and blindness may result

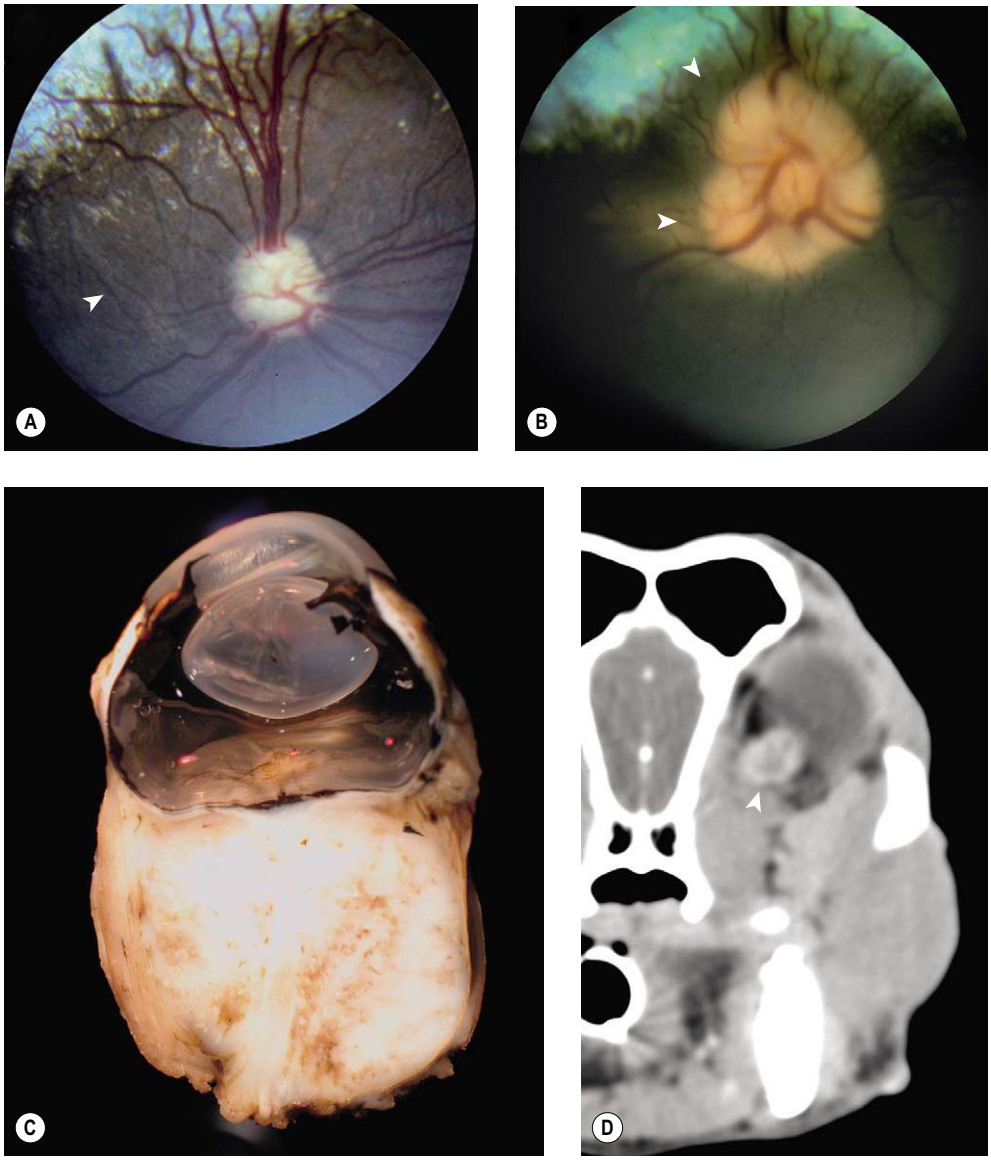


Figure 12.13 Canine orbital meningioma. (A) Miniature Schnauzer, 7 years old: this dog was blind for 1 year and then died during a seizure. Histopathology confirmed a meningioma involving the cerebrum and optic chiasm. The optic disc is pale and demyelinated. Striae of abnormal pigment are also present (arrows). (B) Boxer, 9 years old: the optic disc is swollen with peripapillary edema (arrows). (C) Gross photograph of a canine globe with a gritty mass lesion broadly attached to the posterior pole of the globe. The mass forms a cone around the optic nerve typical of canine orbital meningioma. (D) CT scan of an affected dog showing a cone of swelling surrounding the optic nerve (arrow).

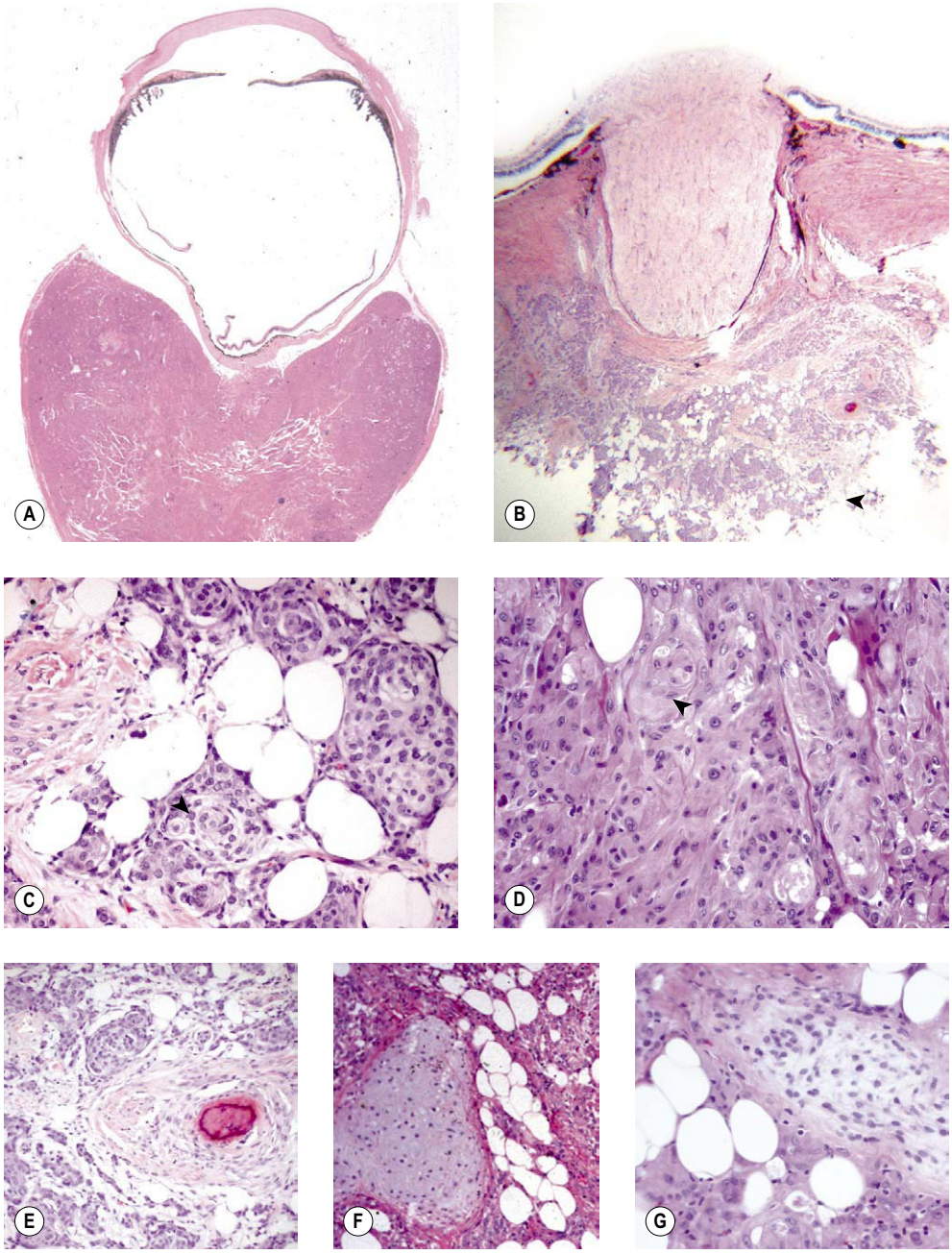


Figure 12.14 Canine orbital meningioma, histopathology. (A) Subgross photograph of a canine globe with orbital meningioma broadly attached to the posterior pole and surrounding the optic nerve. (B) Low magnification photomicrograph showing a canine optic nerve surrounded by a neoplasm. Infiltration into the adjacent loose connective tissue and adipose tissue is a characteristic feature (arrow). (C,D) Photomicrographs showing clusters of the characteristic large epithelial-like tumor cells of canine orbital meningioma (arrows). (E–G) Three photomicrographs showing foci with mesenchymal metaplasia: bone (E), cartilage (F) and myxomatous matrix (G).

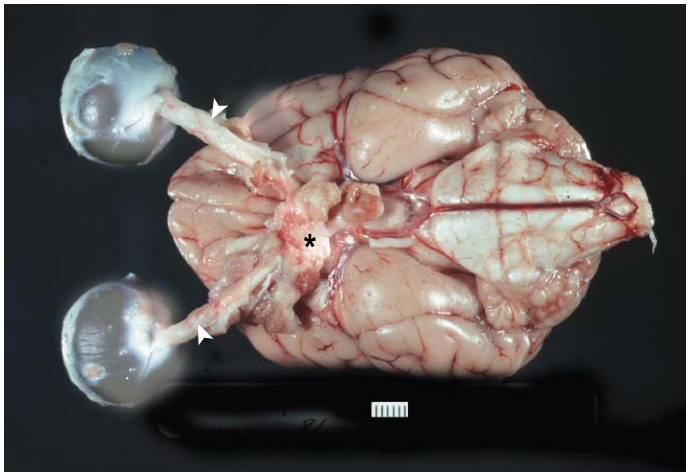


Figure 12.15 Extension of meningioma from the calvarium into the optic nerve. Gross photograph showing the brain from a dog with a ventral meningioma (*) extending down the optic nerve meninges on both sides (arrows).

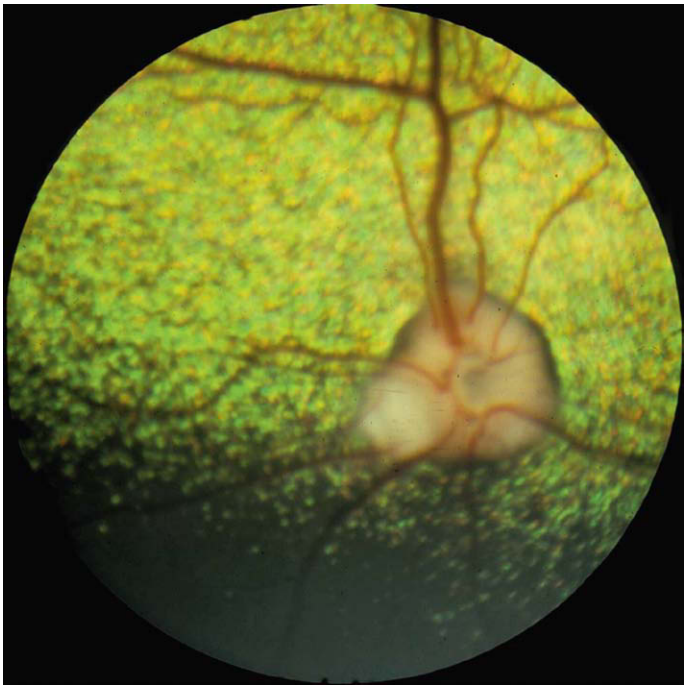


Figure 12.16 Optic nerve glioma, fundus. Saint Bernard, 5 years old: the white elevation on the disc margin was diagnosed as a glioma. It involved the optic nerve and optic chiasm in this blind dog.

Morphologic features of optic nerve head medulloepithelioma in horses include:

- Medulloepithelioma is characterized by the presence of thick tubular rosettes, with a complex cellular lining that is several cells thick and a distinct lumen
- More simple Flexner–Wintersteiner or Homer–Wright rosettes may also be identified in medulloepithelioma but they are not the defining feature
- The neoplasm may also arise from the neuroepithelium of the anterior uvea or, theoretically, the neural retina (see Chapters 9 and 11 for more detailed discussion of the morphologic and immunohistochemical features of medulloepithelioma).

Proliferative optic neuropathy in horses

- These unilateral, benign lesions of the optic nerve head are not uncommon in older horses and do not appear to have a significant impact on vision
  - Due to their benign nature, and appearance in older animals, enucleation and submission to a pathology service is seldom considered and there are no examples in the COPLOW collection
- The clinical appearance is of a well-defined, pedunculated white mass protruding from the optic nerve head into the vitreous cavity, that appears static or very slowly progressive
- Published reports have presented similar morphological features, but alternate diagnoses for proliferative optic neuropathy
  - Large, thin-walled cells with foamy cytoplasm have been described, that were thought to contain lipid
- The lesion should be distinguished from traumatic, exudative optic neuropathy which is associated with loss of vision, and from glioma/astrocytoma (see above).

Comparative Comments

- The two major tumors of the human optic nerve are glioma and meningioma, both of which most commonly affect the retrobulbar portion of the optic nerve
- The most common type of astrocytoma is the juvenile pilocytic astrocytoma
  - These are usually low-grade tumors that occur in the first decade of life
- More than 10% of human patients with optic nerve astrocytomas have neurofibromatosis (NF1)
- Meningiomas of the optic nerve may occur at any age but predominate in middle age and in females
  - They may be unilateral or bilateral and are frequently associated with independent meningiomas within the cranium
  - Tumor growth is slow, and the tumor may invade the optic nerve itself and the eye
  - Microscopically, optic nerve meningiomas are usually of the meningotheliomatous type, with compact masses of protoplasm-rich cells arranged in whorls. Laminated and calcareous concretions (psammoma bodies) are common
- Other less common tumors that principally affect the optic nerve head are melanocytoma, peripapillary choroidal melanoma, pigment epithelial neoplasms, and hemangioma. Leukemic or lymphomatous infiltration of the optic nerve is occasionally seen. Local extension into the optic nerve from retinoblastoma is common, and carcinomatous metastases to the optic nerve have also been reported.

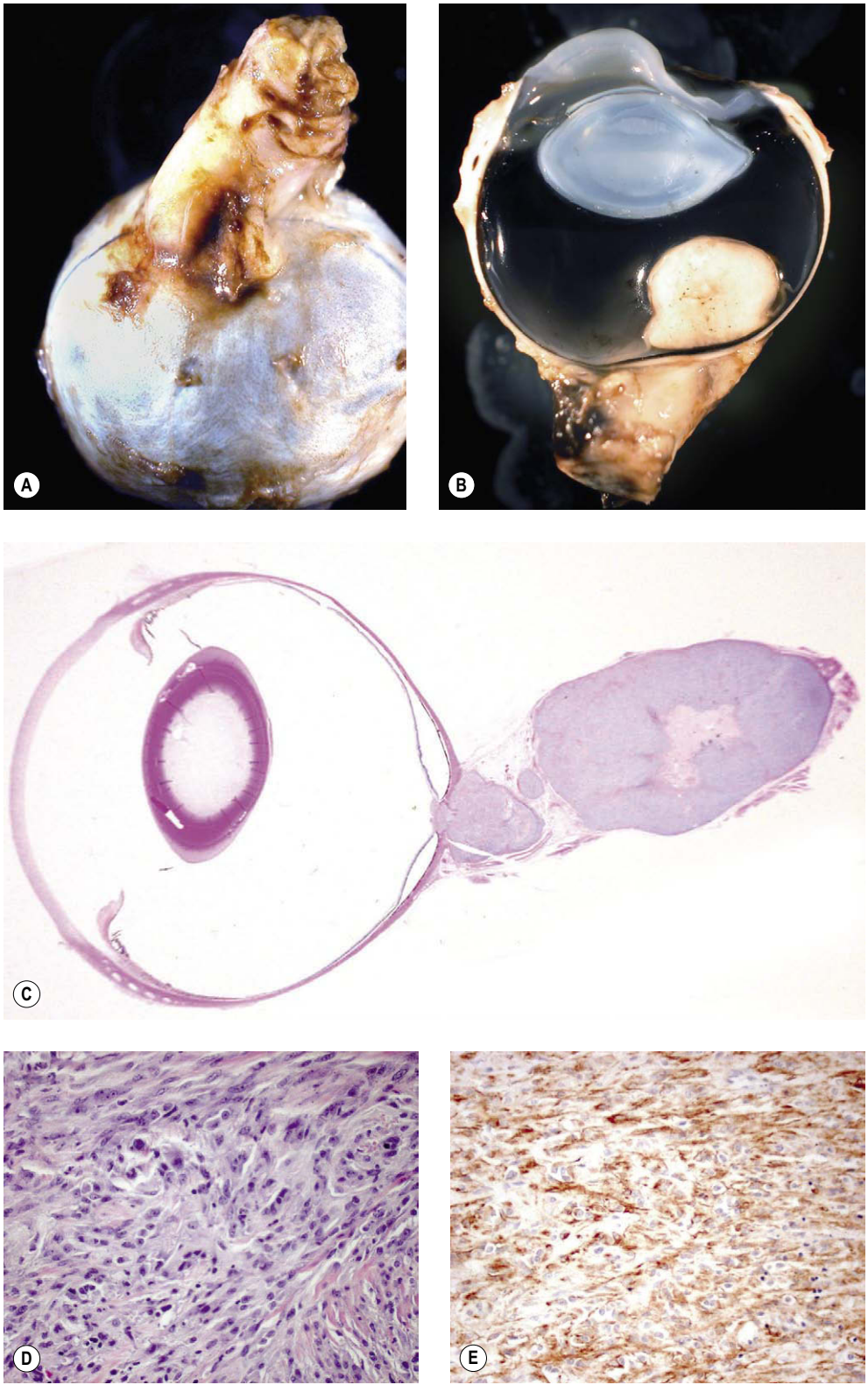


Figure 12.17 Optic nerve glioma, pathology. (A,B) Gross photographs of the same dog eye showing a swollen, neoplastic optic nerve (astrocytoma) bulging into the globe. (C) Subgross photomicrograph showing an optic nerve effaced by an astrocytoma. (D,E) Photomicrographs showing the spindle cell appearance of an optic nerve astrocytoma and GFAP-positive staining (E).

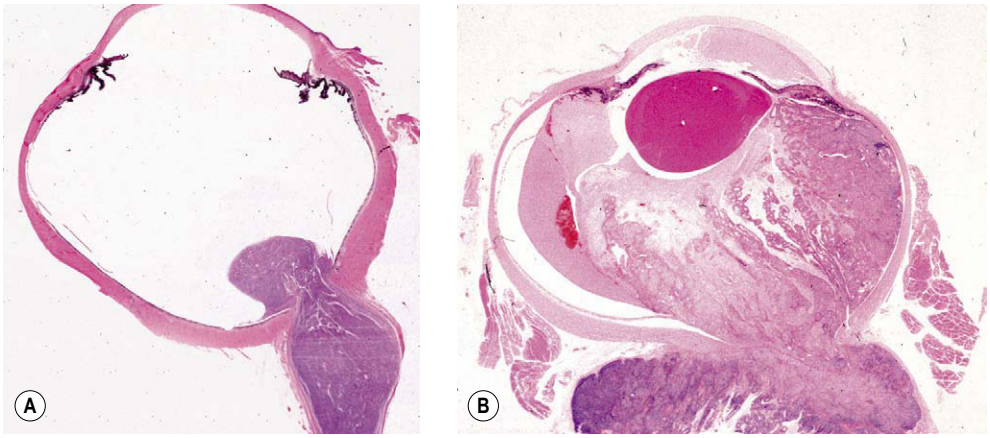


Figure 12.18 Equine optic nerve medulloepithelioma. (A,B) Subgross photomicrographs showing two equine optic nerve medulloepitheliomas effacing the optic nerve and extending into the globe and orbital tissue.

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Chapter 13

The Glaucomas

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GENERAL CONSIDERATIONS

Structure and function of the normal aqueous outflow pathways (Fig. 13.1)

Maintenance of a physiologic intraocular pressure relies on a delicate equilibrium between aqueous humor production and outflow.

- Aqueous is produced by the ciliary processes, by a combination of mechanisms including diffusion, ultrafiltration and active secretion, into the posterior chamber
- From the posterior chamber, aqueous flows through the pupil into the anterior chamber, then enters the ciliary cleft via spaces within the pectinate ligament, which spans the irido-corneal angle (ICA)
- Within the ciliary cleft, aqueous humor percolates through spaces between collagenous beams of the ciliary cleft, then the corneoscleral trabecular meshwork (TM). The corneoscleral TM is embedded in the sclera and closely associated with the collector vessels of the angular aqueous plexus, which are analogous to the annular 'Schlemm's canal' of primates
- Fluid is then transported by a pressure dependent mechanism, via the vacuolating endothelium of the angular aqueous plexus, to the radially oriented collector channels of the intrascleral venous plexus. From there, aqueous passes into the scleral and choroidal veins
- In addition to pressure dependent 'conventional' drainage via the trabecular meshwork into intrascleral and episcleral veins, aqueous can also percolate via a posterior 'uveoscleral' route through the ciliary body interstitium to the suprachoroidal

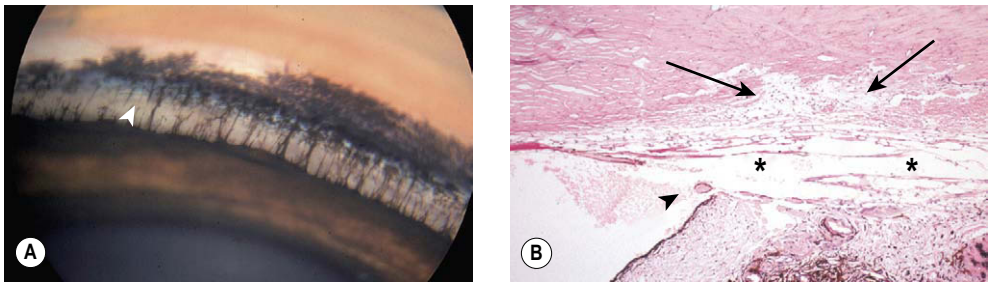


Figure 13.1 Normal canine irido-corneal angle structures. (A) Beagle cross, 4 years old: the pectinate ligaments span the angle from the base of this iris to Descemet's membrane. The superficial and deep pigmented bands are present. The uveal trabeculae (arrow) are easily seen within the ciliary cleft. (B) Photomicrograph of the normal canine irido-corneal angle showing the primary pectinate ligament (arrowhead), ciliary cleft (*) and corneoscleral trabecular meshwork (arrows).

space and vortex veins. Uveoscleral outflow has been estimated to account for about 3% of aqueous outflow in normal cats, and about 15% of aqueous outflow in normal dogs.

The glaucomas: significance and general principles

Definition

The glaucomas represent a large, diverse group of pressure dependant neurodegenerative disorders, that all result in loss of normal function and integrity of the retinal ganglion cells and their axons in the optic nerve and ultimately lead to loss of vision.

- In veterinary patients, the single most consistently recognized feature of all glaucomas characterized to date is elevation in intraocular pressure (IOP).

Significance to a mail-in ocular pathology service

- Glaucoma leads to loss of vision, with varying degrees of ocular pain or discomfort. Despite advances in medical and surgical therapy, the prognosis for restoration and maintenance of vision remains quite poor. Given this relatively poor prognosis for vision, and that therapy can be costly for control of a disease that is often a source of significant discomfort, glaucoma is a common reason for enucleation and subsequent submission of the globe to a pathology service
- 41% of canine submissions to COPLOW have glaucoma as a part of the syndrome
- 29% of feline submissions to COPLOW have glaucoma as a part of the syndrome
- Glaucoma is probably under-represented in equine submissions. The condition often goes clinically undiagnosed in horses as tonometry is less frequently performed in this species and the pain of glaucoma is not manifest as acutely as it is in dogs.

Non-specific changes in ocular tissues associated with elevated intraocular pressure (Fig. 13.2)

Many of the changes listed below can represent either a cause or an effect of glaucoma. It is often difficult to determine which, with confidence.

- Cornea and sclera
  - Corneal edema
  - Descemet's streaks (Haab's striae) associated with tears or splits in Descemet's membrane
  - Corneal vascularization
  - Scleral atrophy at the limbus
  - Thinning, stretching and enlargement of the globe (buphthalmos)
    - This is more commonly seen in animals than in humans with glaucoma
    - Globe enlargement is more dramatic in young animals and children than in adults
  - Equatorial and limbal staphyloma
- Uvea
  - Collapse of the ciliary cleft
  - Atrophy of the corneoscleral trabecular meshwork
  - Iris atrophy
  - Ciliary body atrophy
  - Decreased choroidal perfusion
- Lens
  - Cataract
  - Lens subluxation or luxation
- Neurosensory retina
  - Loss of retinal ganglion cells (all species)
  - Full thickness retinal atrophy and gliosis, dogs only
  - Less atrophy of the superior (tapetal retina relative to the inferior (non-tapetal) retina, dogs only
- Optic nerve
  - Necrosis is an early feature, followed by malacia, gliosis and the formation of a deep cup. In species other than the dog the development of gliosis and cupping follows a less precipitous course
  - In glaucomatous optic neuropathy, there is a loss of large diameter optic nerve axons.

Underlying pathogenesis

It can be challenging for the pathologist to differentiate primary and secondary changes and suggest the underlying pathogenesis, in the absence of an informative clinical history. For example, lens subluxation may lead to, or result from, glaucoma. Consideration of breed predispositions may increase the index of suspicion for either primary or secondary causes of glaucoma.

Critical events in the pathogenesis of the glaucomas

Many of the critical events in the pathogenesis of the glaucomas remain poorly understood including the following:

- The precise mechanism responsible for the control and regulation of intraocular pressure, particularly at the level of aqueous outflow, is incompletely understood in both normal and glaucomatous animals.

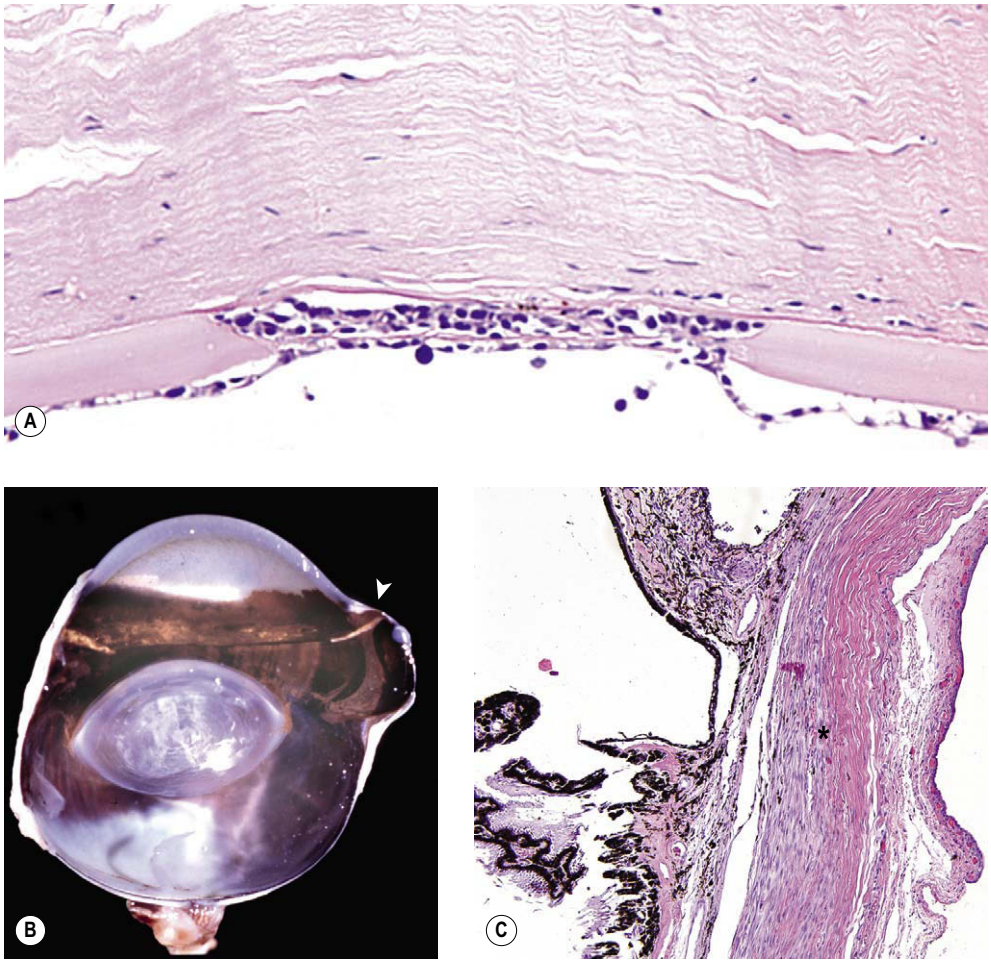


Figure 13.2 Non-specific morphologic features of glaucoma (A) Photomicrograph of a canine cornea showing Haab's stria in glaucoma (B) Gross photograph of a dog eye showing an acquired staphyloma at the limbus (arrow). (C) Photomicrograph of the irido-corneal angle and the limbal sclera from a dog with glaucoma showing a loss of collagen associated with scleral atrophy (*).

Mechanisms for IOP elevation

- To date, no instances of glaucoma related to increased aqueous humor formation have been documented in veterinary glaucoma patients
- The key mechanisms for IOP elevation are therefore:
  - Reduction in capacity for aqueous outflow, and/or
  - Increase in episcleral venous pressure (i.e. 'back pressure')
- Reduction in the capacity for aqueous outflow may be:
  - Primary (goniodysgenesis):
    - Due to an inherent abnormality in the aqueous outflow pathways
      - It is worth emphasizing that the cause of increased resistance in the aqueous outflow pathway in goniodysgenesis is not yet known. The possibility that aqueous outflow obstruction might actually prove to be secondary and not primary cannot be discounted
    - Primary glaucoma is fairly common in certain breeds of dog
    - Primary glaucoma is seldom encountered in other domestic species
  - Secondary to other ocular or systemic disease processes, as a relatively frequent complication of:
    - Uveitis
    - Synechiae
    - Pre-iridal fibrovascular membrane
    - Cataract
    - Lens luxation
    - Intraocular neoplasia
    - Intraocular hemorrhage
    - Retinal detachment
- Increase in episcleral venous pressure may occur:
  - In animals with orbital space occupying lesions
  - Transiently, as a result of inappropriate restraint restricting jugular blood flow, including tight collars
- Mechanisms for aqueous outflow obstruction:
  - Pupil block
    - Anterior lens luxation, anterior vitreous prolapse, intumescent cataract and extensive posterior synechiae are all relatively common causes of pupil block glaucoma
    - Flow of aqueous humour from the posterior chamber to the anterior chamber is obstructed at the level of pupil and aqueous is therefore unable to exit through the conventional outflow pathways via the irido-corneal angle and ciliary cleft
    - Elevation in pressure within the posterior chamber leads to forward displacement of the iris, collapse of the ciliary cleft, narrowing of the irido-corneal angle and a shallow anterior chamber. The anterior chamber may be diffusely shallow, or may vary in depth as in iris bombé.

- Angle closure
  - Secondary angle closure glaucoma may occur as a sequela of pupil block, as the iris is 'pushed forward', occluding the opening of the irido-corneal angle. Multiple iridociliary cysts, as sporadically encountered in the Golden Retriever and Great Dane breeds, may also lead to anterior displacement of the ciliary zone of the iris contributing to secondary angle closure
    - Theoretically, in such cases, it should be possible to 'open' the angle during indentation gonioscopy, but as the ciliary cleft collapses, angle closure can become permanent
  - Alternatively, the iris may be 'pulled forward', as occurs in association with contracture of pre-iridal fibrovascular membranes (PIFVM), in a mechanism that can ultimately lead to extensive peripheral anterior synechiae
  - Obstruction of the trabecular meshwork and/or obliteration of the ciliary cleft by cellular infiltrates or debris may lead to the development of glaucoma secondary to neoplasia, uveitis and intraocular hemorrhage

- Clinical and pathological nomenclature: open-angle versus closed-angle
  - Traditionally, veterinary ophthalmologists have tended to classify glaucomas clinically, on the basis of gonioscopic findings, as either 'open-angle' or 'closed-angle'. In reality, what we are really referring to is not simply the irido-corneal angle (ICA), but the opening to the ciliary cleft
  - In contrast, veterinary pathologists have tended to classify many of the primary glaucomas as 'open-angle, closed-cleft'. This has led to confusing discrepancies in the clinical and histopathological classification of the canine and feline glaucomas
  - Until relatively recently our ability to visualize and clinically characterize the ciliary cleft *in vivo* was extremely limited. Refined imaging techniques, such as ultrasound biomicroscopy (UBM), with probe frequencies around 50 MHz, and high resolution ultrasonography (HRUS), with probe frequencies around 20 MHz, offer us a greater appreciation for the dynamic changes that take place within the aqueous outflow pathways in our glaucomatous patients. These new technologies should facilitate the harmonization of clinical and pathological classification schemes as well as improve our insight into the pathogenic mechanisms involved in each individual patient

Because of the confusion, in this chapter we will avoid the use of this terminology altogether.

Mechanisms of optic nerve and retinal damage

The mechanisms of optic nerve and retinal damage in the glaucomas remain subject to debate. Proposed mechanisms include the following:

- Elevated intraocular pressure leads to deformation of the optic nerve axons at the lamina cribrosa and the blockage of anterograde and retrograde axonal transport which, in turn, leads to the death of retinal ganglion cells. Cell death is due, at least in part, to an interruption in the supply of neurotrophic factors from the CNS
- Elevated intraocular pressure leads to deformation of the lamina cribrosa, leading to a decrease in vascular perfusion of the optic nerve head microcirculation, that results in a loss of axonal integrity and subsequent death of retinal ganglion cells
- Elevated intraocular pressure leads to tissue infarction and subsequent gliosis
- Retinal ganglion cell loss may also be due to the pathologic release of glutamate from within the damaged retina, which initiates the process of apoptosis by a mechanism termed 'excitotoxicity'
- Decreased choroidal perfusion causes a segmental retinal degeneration affecting both inner and outer retina
- Recent evidence suggests that different mechanisms may be involved in the death of the retinal ganglion cell bodies, axons and dendritic trees.

Mechanisms of retinal and optic nerve degeneration

The relevance of the various proposed mechanisms of retinal and optic nerve degeneration to the spontaneous glaucomas of dogs and cats:

- Any or all of these proposed mechanisms might be in play, depending on the species and also the underlying pathophysiology of the different glaucoma syndromes in dogs and cats
- The pathogenic mechanisms in play, and their relative importance, appear to differ considerably between glaucomatous dogs, cats and humans
  - In the dog, the changes in the retina and the optic nerve head suggest that abnormal vascular perfusion and ischemia are major factors in the pathogenesis of optic nerve and retinal damage encountered in glaucoma syndromes. Severe damage to the inner and outer retina and optic nerve can be observed in dogs at a very acute stage of disease. In acute congestive canine glaucoma, where IOP is frequently >50 mmHg, there is evidence to support an important role for ischemia in cell death within both the inner and outer retina. Breakdown in the blood-ocular barrier and inflammation may also contribute to retinal degeneration
  - In the cat, the retinal disease is more restricted to the ganglion cell layer, and optic nerve necrosis and malacia is less common.

Comparative Comments

As is the case in other animal species, 'glaucoma' in human ophthalmology is generally considered a generic term for a common group of ocular diseases that, if untreated, can cause an irreversible loss of visual function. The common underlying factor in all forms of glaucoma is an inappropriate intraocular pressure, which is associated with damage to the retina and optic nerve head.

Glaucoma in humans is usually divided into five main categories:

1. Congenital glaucoma
2. Primary open-angle glaucoma
3. Primary angle-closure glaucoma
4. Secondary open-angle glaucoma
5. Secondary closed-angle glaucoma.

Unlike the situation described with canine and feline glaucoma, in developed countries enucleation is practically never carried out for uncomplicated primary open-angle glaucoma. It is, however, sometimes performed for the secondary types of glaucoma, particularly in cases of tumors, vascular disease, uveitis, and trauma.

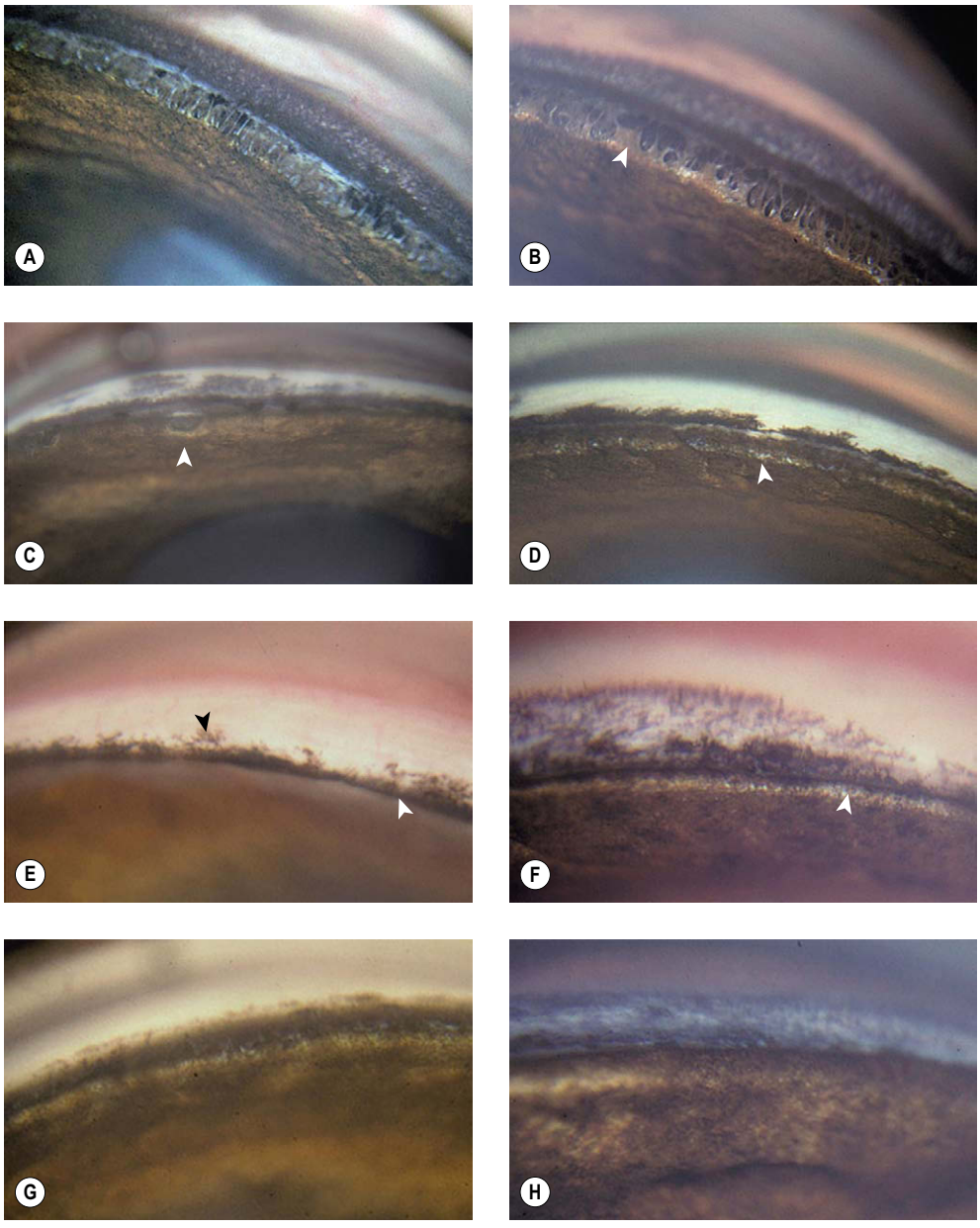


Figure 13.3 Gonioscopy of the canine irido-corneal angle, normotensive eye, in goniodysgenesis. The following examples represent the 'normotensive' eye in cases presented with unilateral glaucoma. The glaucomatous eye was histopathologically diagnosed as goniodysgenesis. (A) Cocker Spaniel, 6 years old: the pectinate ligaments have a thick iris base. (B) Cocker Spaniel, 6 years old: the base of the pectinate ligaments is wide (arrow). This has been termed 'truncated' pectinate ligaments. (C) Cocker Spaniel, 9 years old: the sheet of pigmented tissue extends over most of the ciliary cleft. The arrow points to what is termed a 'flow hole' in this extensive sheet. (D) Cocker Spaniel: 6 years old: the fine white areas (arrow) represent small open areas in the heavily pigmented tissue. (E) Australian Cattle Dog, 4 years old: only the superficial pigmented band (black arrow) can be seen. The iris is 'bowed' forward occluding the view of the irido-corneal angle (white arrow). (F) Basset Hound, 4 years old: no normal pectinate ligaments could be visualized. The white band (arrow) may represent the ciliary cleft. (G) Dalmatian, 7 years old: the pigmented band covers the entire angle recess. (H) Bullmastiff, 2 years old: no ciliary cleft was visible. The bluish color may represent limbal corneal edema.

THE CANINE GLAUCOMAS

Goniodysgenesis associated glaucoma (primary glaucoma, acute primary angle-closure glaucoma, primary open-angle closed-cleft glaucoma) (Figs 13.3, 13.4)

- The defining features of goniodysgenesis (pectinate ligament dysplasia, mesodermal dysgenesis)
  - This is a familial, breed-related, congenital abnormality in the structures of the irido-corneal angle (ICA) and aqueous outflow apparatus
    - Commonly affected breeds include the Bassett Hound, English and Welsh Springer spaniel, Flat-coated retriever, Great Dane, Samoyed, Sheba Inu and Siberian Husky
  - Goniodysgenesis is characterized, morphologically, by the following features:
    - A solid iris-like sheet of uveal stroma extending from the iris base to the arborized termination of Descemet's membrane (pectinate ligament dysplasia)
    - The abnormal sheets of uveal tissue are intermittent, and width of the irido-corneal angle and opening of the ciliary cleft can vary considerably throughout its circumference
      - The extent of goniodysgenesis is therefore best assessed by clinical observation of both the width of the opening of the ciliary cleft and the appearance of the pectinate ligament, using a special lens placed on the cornea (gonioscopy)
      - The glaucomatous eye cannot be used to observe the extent of goniodysgenesis because the cornea becomes cloudy with edema and the irido-corneal angle is

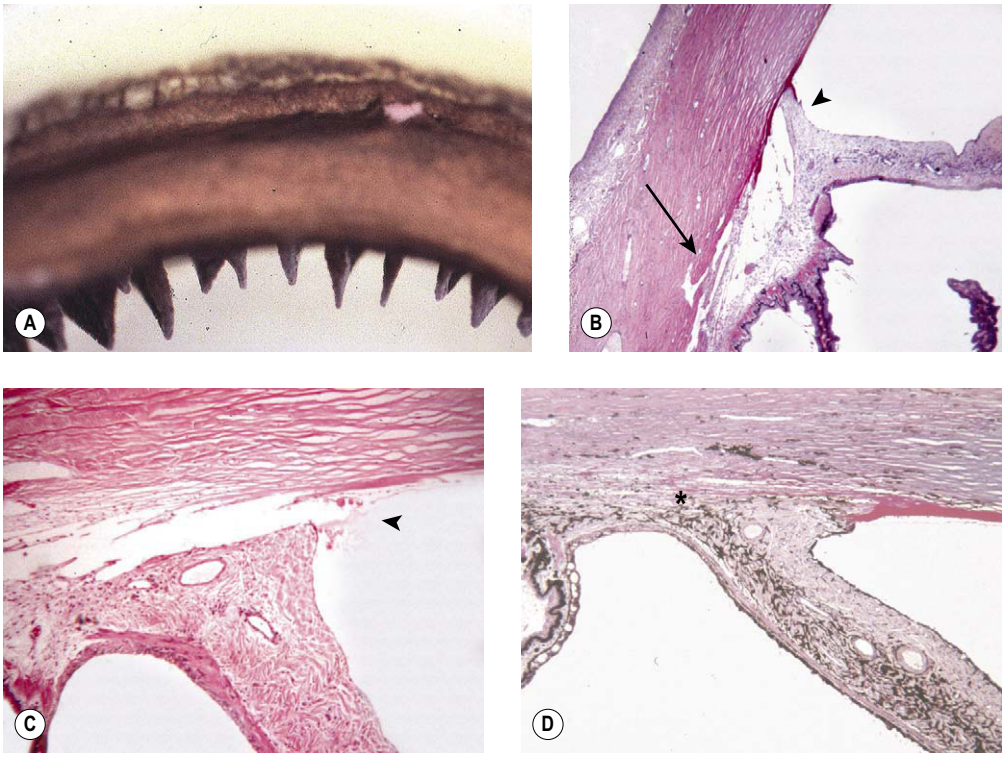


Figure 13.4 Goniodysgenesis, pathology. (A) Gross photograph showing a canine irido-corneal angle with goniodysgenesis from a normotensive globe. (B) Photomicrograph of a normotensive eye with goniodysgenesis showing a solid membrane of iris-like tissue spanning the angle (arrowhead). The ciliary cleft and the corneoscleral trabecular meshwork (arrow) are normal in this normotensive eye. (C) Photomicrograph of goniodysgenesis sectioned through a small opening (arrow). (D) Photomicrograph of a canine angle with goniodysgenesis and glaucoma. The iris-like membrane is in front of a collapsed ciliary cleft (*) and the corneoscleral trabecular meshwork is not apparent. The terminus of Descemet's membrane showing characteristic thickening and branching.

narrowed by elevated IOP. The unaffected contralateral eye is used to evaluate the extent of affected angle
    - Severity or grade of goniodysgenesis appears to be heritable
    - The greater the extent of circumferential involvement of the drainage angle, the greater the chances of developing glaucoma
- Severe goniodysgenesis is clearly a risk factor in the development of glaucoma but most dogs affected by goniodysgenesis do not develop glaucoma
  - Although gonioscopy may reveal goniodysgenesis or pectinate ligament dysplasia (PLD) in a significant number of dogs within certain breeds, only some of these animals will actually go on to develop glaucoma. The pectinate ligament is clearly *not* the most important source of resistance to aqueous outflow
  - However, goniodysgenesis may signal the existence of other developmental abnormalities within the structures of the ciliary cleft or may have implications in the way the iris is positioned during miosis and mydriasis perhaps predisposing to pigment dispersion
  - The limitation of gonioscopy in our clinical evaluation of the canine aqueous outflow pathway has been highlighted by histopathological identification of goniodysgenesis and ciliary cleft collapse in Norwegian elkhounds, a breed previously classified as affected by a chronic, slowly progressive, 'open-angle' glaucoma
- A dog with goniodysgenesis-related glaucoma in one eye is highly likely to develop glaucoma in the second eye
  - For this reason there is a lot of interest in 'prophylactic' treatment which might delay or prevent glaucoma development in the second eye

- From 'at risk' to acute glaucoma – pathogenic mechanisms in dogs with goniodysgenesis
  - In dogs with goniodysgenesis, the progression to an acute glaucomatous crisis characteristically does not occur until middle age or later in life
    - There is a suspicion that in many affected dogs, transient episodes of IOP elevation, with subsequent spontaneous resolution, precede confirmed glaucomatous crises. There are competing hypotheses which attempt to explain the increased intraocular pressure
    - Elucidating the mechanisms that precipitate acute IOP elevations in dogs with goniodysgenesis will greatly enhance our ability to treat, and hopefully prevent or delay the onset of, glaucoma in 'at-risk' eyes
  - Severe goniodysgenesis, narrow ICA, relatively anterior lens position, thick lens, and shallow anterior chamber, may all be considered as anatomic risk factors, i.e. markers indicating predisposition to glaucoma
    - Similar anatomic risk factors may predispose human and canine subjects to primary angle closure glaucoma. However, only a small proportion of individuals with these characteristic risk factors go on to develop glaucoma
  - Age-related changes in morphologic features such as lens thickness and narrowing of the irido-corneal angle may, at least in part, contribute to angle closure and the development of glaucoma in middle-aged and older dogs
  - Acute pupil block is a dynamic process that has also been put forward as a factor contributing to acute glaucomatous crises. It has been proposed that a very small segment of the iris, right at the pupil margin, is held in apposition against the anterior lens capsule by a complex dynamic mechanism that involves 'iris stretch' and combined 'blocking forces' generated by both the sphincter and dilator muscles.
    - A role for 'iris touch', i.e. iris-lens contact, in the pathogenesis of IOP elevation in dogs with

goniodysgenesis-related glaucoma is supported by the finding of pigment dispersion in affected eyes
- Significant uveal inflammation was also identified in canine eyes with acute glaucoma. Whether uveitis plays a role in precipitating episodes of glaucoma due to iris thickening or miosis, or whether inflammation is a secondary phenomenon in dogs with primary glaucoma remains unclear
  - Resistance to the flow of aqueous caused, in some way by the abnormal uveal membranes or by matrix deposited by the membrane
  - Obstruction of aqueous drainage at the level of the pupil associated with contact between the papillary margin of the iris and the lens
  - Degeneration of the filtration apparatus secondary to entrapment of released melanin
  - Any combination of mechanisms
- Histopathological studies are associated with important limitations, including the tendency to examine only globes obtained at a late stage in the disease process
- Disease progression in canine goniodysgenesis-associated glaucoma begins with the sudden development of severe disease. Morphologically, the disease progresses in a stepwise manner, consistent with a rapidly progressive disease course following a dramatic initiating event

Sequential changes in the drainage angle following acute IOP elevation in goniodysgenesis-related glaucoma

The first 24 h (Fig. 13.5)

- Atrophy of the corneoscleral trabecular meshwork
  - The identification of this change, so soon after the apparent onset of acute glaucoma, suggests that there is latent disease building up to the glaucomatous crisis
- Incomplete collapse of the ciliary cleft
- Disruption of the posterior pigmented epithelium of the iris near the pupillary margin
- Free pigment granules within the anterior chamber and in the angle and trabecular meshwork
- Neutrophilic inflammatory cell infiltrate in the anterior chamber, irido-corneal angle, ciliary cleft and the limbal sclera
- Nuclear enlargement and increased mitotic activity involving stromal fibroblasts and endothelial cells at the limbus

1–5 days (Fig. 13.6)

- Complete closure of the ciliary cleft with indistinguishable corneoscleral trabecular meshwork
- Dispersion of pigment remains a prominent feature within the anterior chamber and filtration angle
- Loss of the posterior pigmented epithelium from the pupillary margin of the iris
- Neutrophilic inflammatory cell infiltrate is rarely seen
- Evidence of cellular proliferation remains apparent within the limbal tissues

Chronic changes (Fig. 13.7)

- Complete collapse of the ciliary cleft with indistinguishable corneoscleral trabecular meshwork
- No neutrophilic inflammation
- Pigment dispersion remains, but rarely at a significant level

Sequential changes in the retina following acute IOP elevation in goniodysgenesis-related glaucoma

The first 24 h (Figs 13.8, 13.9)

- Radiating sectors of edematous retina apparent grossly
- Hypereosinophilic, necrotic retinal ganglion cell profiles seen
  - This change is seen rarely at later stages, in association with more chronic disease, suggesting that retinal degeneration can occur as a cyclic or ongoing process
- Outer retinal edema but no cellular necrosis or apoptosis
- Müller cell expression of glial fibrillary acidic protein (GFAP) is little changed from background
- Neutrophilic inflammatory cell infiltrate in the retinal tissue

1–5 days (Fig. 13.10)

- Radiating zones of retinal edema and degeneration still apparent grossly
- Extensive, segmental, full-thickness retinal cell apoptosis. The pattern of regionally variable severity correlates with the radiating pattern of edema and degeneration seen grossly
- Segmental full-thickness retinal degeneration and necrosis is characteristic in dogs with acute goniodysgenesis-related glaucoma, but is not a typical feature associated with glaucoma in any other species
- Marked upregulation in the expression of GFAP by Müller cells and astrocytes
- Degenerative changes often appear more advanced within the dependant, non-tapetal, retina (a phenomenon referred to as 'tapetal sparing')

Chronic changes (Fig. 13.11)

- Full thickness retinal atrophy with elevated expression of GFAP
- The process of apoptosis continues far beyond 5 days, and rarely, hypereosinophilic ganglion cells, interpreted as necrotic but not apoptotic, are seen even in long standing disease
- The relative sparing of the superior retina is most prominently seen in the eyes of chronically glaucomatous dogs
  - Although this phenomenon is called 'tapetal sparing', in atapetal dogs there is still relative sparing of the superior retina

Sequential changes in the optic nerve following acute IOP elevation in goniodysgenesis-related glaucoma

The first 24 h (Fig. 13.12)

- Swelling of the optic nerve head
- Necrotic neuropil with a few phagocytic cells (gitter cells)
- This change can be hard to appreciate because the neuropil is not very cellular to begin with
- Granular neuropil remnants often protrude into the vitreous
- Neutrophils within the neuropil of the optic nerve head

2–5 days (Fig. 13.13)

- Malacia of the optic nerve head
  - Gitter cells predominate
  - With the phagocytosis of optic disc neuropil, the tissue becomes cavitated
- Vitreous matrix is often incorporated into the cavitated optic nerve (Schnabel's cavernous atrophy)

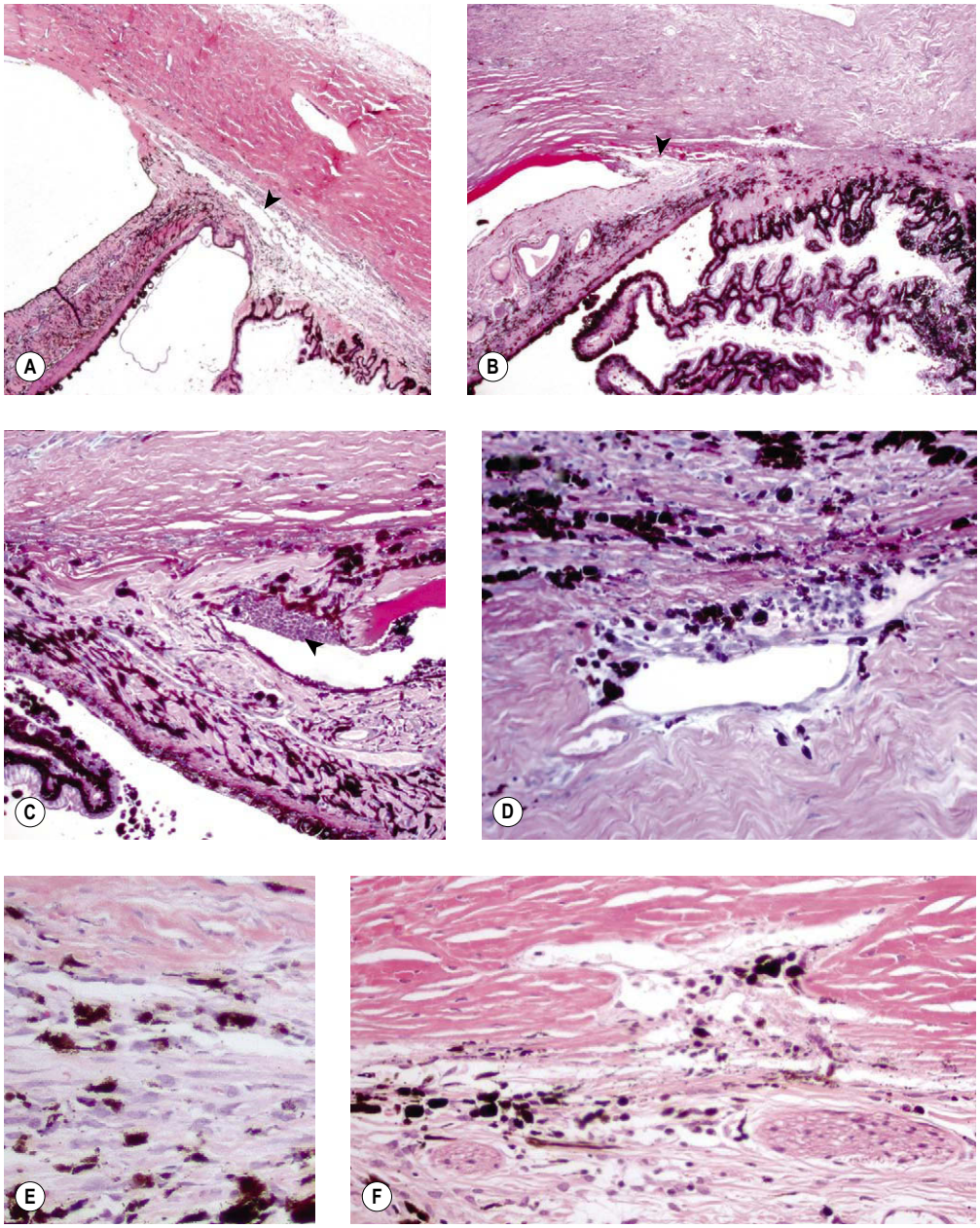


Figure 13.5 Goniodysgenesis, pathology of acute disease. (A,B) Low magnification photomicrographs showing the canine irido-corneal angle from a dog with clinical signs of glaucoma for only 2 days. The ciliary cleft is still apparent, but not the corneoscleral trabecular meshwork (arrows). (C) This irido-corneal angle is from a dog with goniodysgenesis within 2 days of the onset of clinical disease. It shows a neutrophilic infiltrate (arrow). (D) The corneoscleral trabecular meshwork, from a dog with clinical glaucoma less than 2 days, shows pigment dispersion and a neutrophil infiltrate. (E,F) Atrophic corneoscleral trabecular meshwork from dogs with acute glaucoma. The structure is severely atrophied and contains excess pigment cells.

Chronic changes (Figs 13.14, 13.15)

- End-stage gliosis, atrophy and cupping of the optic nerve head
- In the progression of optic nerve cupping in dogs the distortion of the nerve head is more a matter of necrosis and collapse than a backwards thrust against the lamina cribrosa of the optic nerve.

Comparative Comments

- Primary angle-closure glaucoma in humans is a form of glaucoma in which there is an anatomic predisposition to obstruction of aqueous outflow by irido-trabecular contact as a result of a narrow angle and/or shallow anterior chamber
- An additional predisposing anatomical feature is a plateau iris
- Other factors include hyperopic eyes, in which the sizes of the lens and the anterior chamber are disproportionate, and small eyes
- Primary angle-closure glaucoma is more common in Eskimos and East Asians, as well as in middle age and in women. There is often a family history
- Attacks of primary angle-closure glaucoma tend to occur when the pupil is in mid-dilatation. Here, greater iris contact with the anterior lens capsule increases resistance to the passage of aqueous humor through the pupil, and this increased resistance displaces the iris root anteriorly. In this situation, angle closure may occur
- On histopathologic examination of an untreated globe with narrow-angle glaucoma, the anterior chamber is seen to be

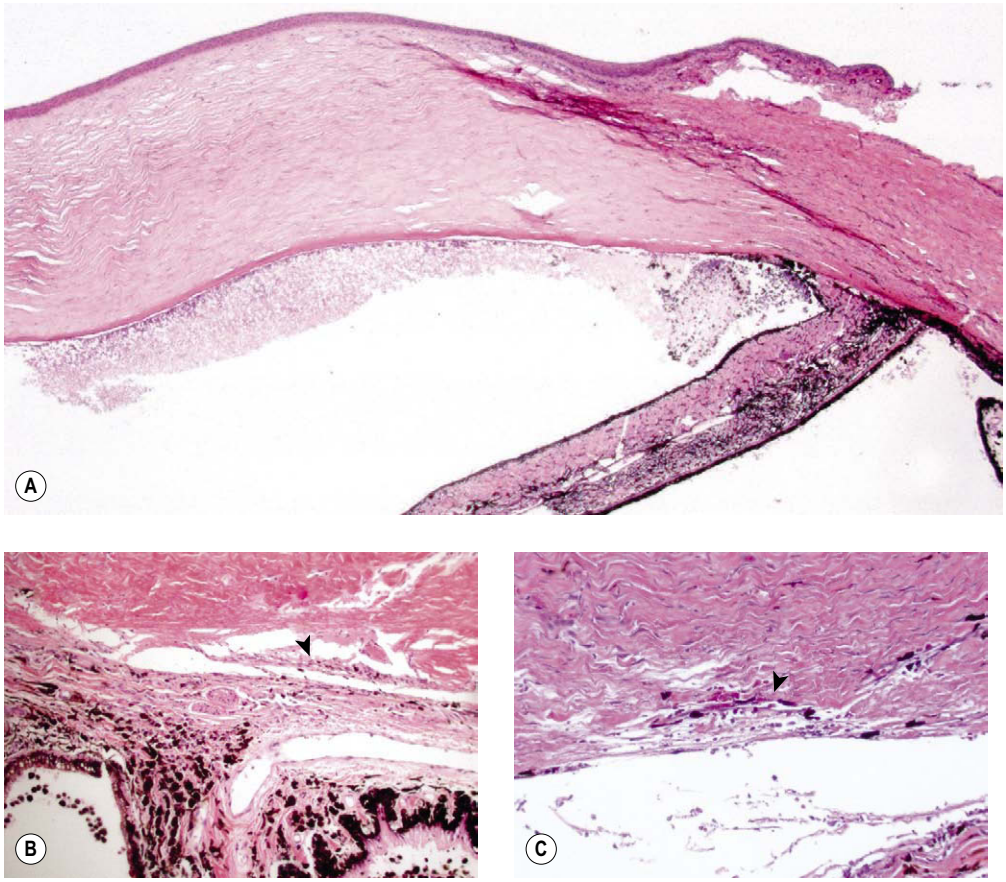


Figure 13.6 Goniodysgenesis and pigment dispersion in acute glaucoma. (A) Low magnification photomicrograph from a dog with a 4-day history of glaucoma and goniodysgenesis showing large amounts of free pigment in the dependent aspect of the anterior chamber and complete collapse of the ciliary cleft. (B,C) Higher magnification photomicrographs showing what remains of the atrophied corneoscleral trabecular meshwork. Notice the pigment in the atrophied structure (arrows).

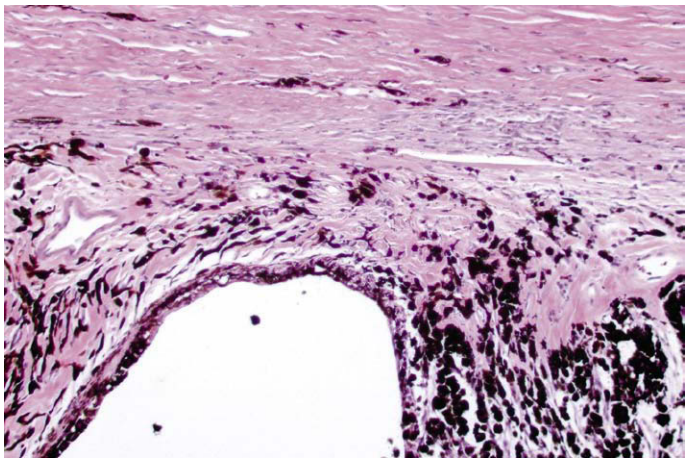


Figure 13.7 Goniodysgenesis, chronic disease. Photomicrograph, from a dog with glaucoma for 1 week or longer, showing the completely collapsed and atrophied ciliary cleft and corneoscleral trabecular meshwork.

Comparative Comments (continued)

narrow and the angle closed. Usually a relatively large lens is evident

- Necrosis of the dilator and sphincter muscles is observed and leads to irregularities in the pupillary shape
- Segmental iris atrophy is often present, together with generalized atrophy of the iris stroma
- Small subcapsular anterior white opacities in the lens (glaukomflecken) are characteristic if there have been multiple attacks
- The corneal epithelium shows damage, and the corneal stroma may be edematous
- Because of blockage of venous return, optic disk edema and even central retinal vein occlusion may be seen
- Commonly, the prolonged contact of the iris with the trabecular meshwork has led to peripheral anterior synechiae (PAS), as well as fibrosis of the trabecular meshwork
- Often there is evidence of laser peripheral iridotomy or surgical iridectomy.

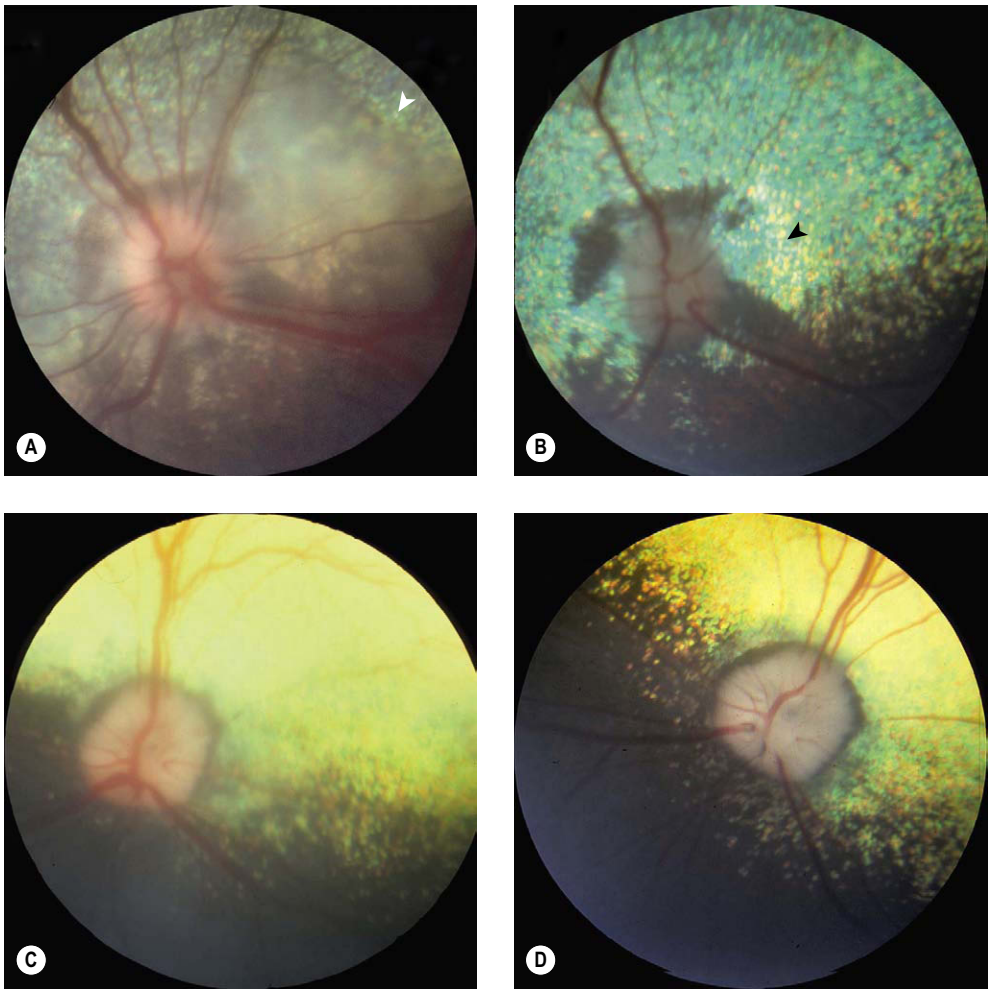


Figure 13.8 Retinal disease in acute goniodysgenesis glaucoma, fundus. (A) Samoyed, 4 years old: the optic disc is swollen and retinal vessels are dilated. The peripapillary retina is edematous and has a large bullous detachment (arrow). (B) The same eye as in (A), 12 days following treatment, is now a normotensive eye. The optic disc is pale. Peripapillary tapetal pigmentation and hyperreflectivity (arrow) are present. The eye was visual. (C) Cocker Spaniel, 8 years old: the peripapillary retina is edematous. The optic nerve changes are discussed in Figure 13.12. (D) This is the same eye as (C), 4 weeks later. The peripapillary retina is atrophic, resulting in tapetal hyperreflectivity. The eye was visual.

Canine primary open-angle glaucoma (POAG)

- Infrequently encountered in practice or submitted to diagnostic pathology services
- Heritable POAG has been extensively studied in Beagles, within a colony of affected dogs at the University of Florida
- Abnormalities in ocular vascular resistance, tonographic aqueous outflow facility (which progressively declines from several months of age) and IOP have been confirmed in affected dogs, prior to the late-stage development of angle closure and advanced glaucoma that occurs from about the third year of life
- Of the few cases that are encountered sporadically in clinical veterinary practice, many are presented once glaucoma is advanced and, in general, histopathological findings are likely to be similar to those seen in primary goniodysgenetic glaucoma
- In Beagles, as in humans with POAG, the precise mechanism for aqueous outflow obstruction remains unclear. However, the site of increased aqueous outflow resistance in POAG appears to reside in the trabecular meshwork and its extracellular matrix. In addition to the accumulation of abnormal, enzyme resistant glycosaminoglycans in the extracellular meshwork of the TM of affected dogs, abnormal amounts of myocilin protein have been identified in eyes of affected Beagles.

Comparative Comments

- Primary open-angle glaucoma (POAG) is by far the most common type of human glaucoma, affecting 1–2% of the population over 40 years of age. If untreated, it can lead to marked visual loss and blindness
- POAG is a chronic, slowly progressive, usually bilateral disease, characterized by an increased resistance to aqueous outflow. There is usually an increased intraocular pressure with associated injury to the retinal ganglion cell axons
- The pathogenesis of this disease is unclear. The microscopic structure of the anterior chamber angle is normal. The histopathology findings related to POAG are controversial, with the changes appearing similar to aging changes, but they appear to be more severe and occur earlier in glaucomatous eyes
- It is generally believed that the disease is multifactorial and results in an imbalance between intraocular pressure and vascular perfusion of the optic nerve head. In addition, mechanical pressure on the ganglion cell axons at the neuroretinal rim may interfere with axonal flow and result in retrograde neuronal degeneration
- Probably a subset of POAG, 'normal tension glaucoma' or 'low tension glaucoma' is a disease in which optic disk cupping, atrophy of the optic disk, and visual field loss may occur in the absence of a demonstrable elevation of intraocular pressure.

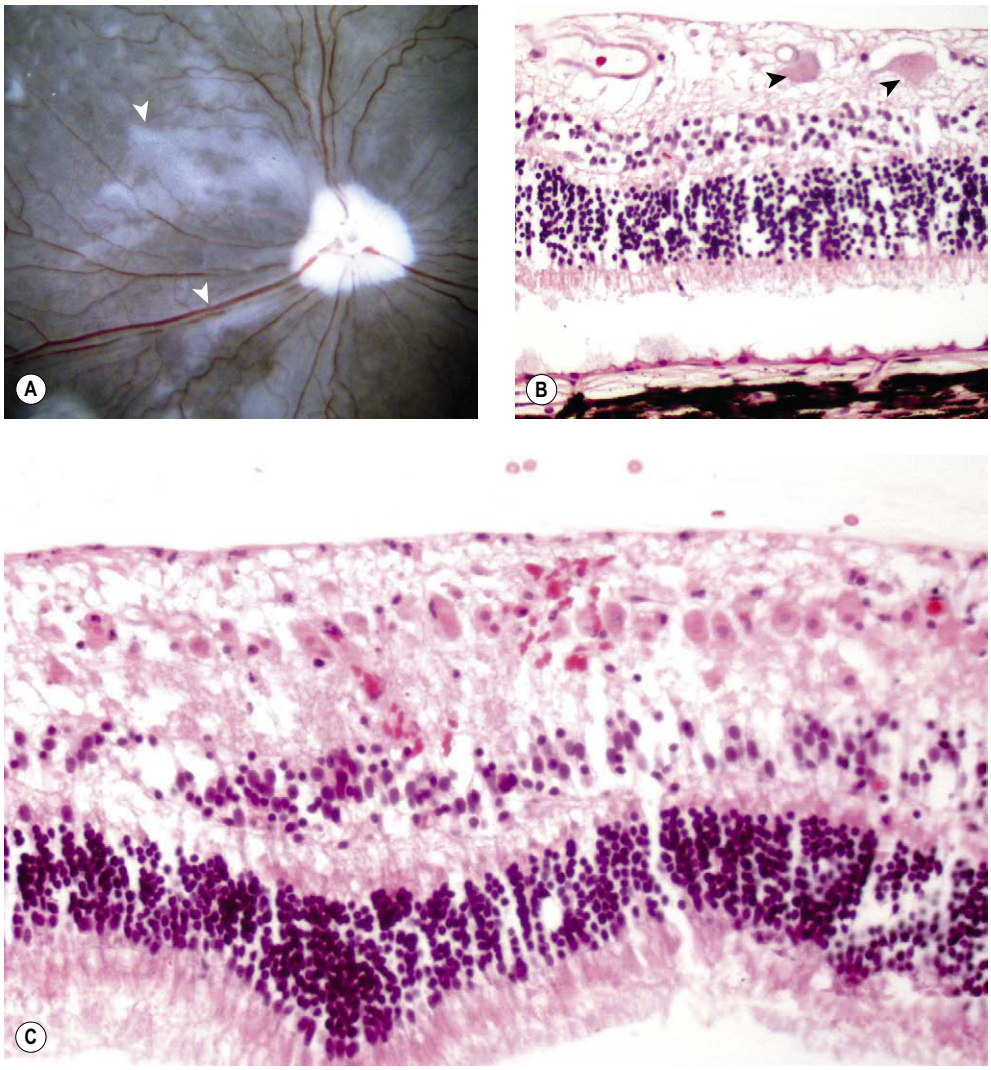


Figure 13.9 Retinal disease in acute goniodysgenesis glaucoma, pathology. (A) Gross photograph of a canine globe posterior segment from a dog with clinical glaucoma for 3 days before enucleation. The globe, which was fixed in glutaraldehyde and opened so that the fundus is visible, showing radiating spokes of translucent retina (arrows). (B) Photomicrograph, of the retina from a dog with glaucoma for 1 day, showing edema and hypereosinophilic necrotic ganglion cells (arrows). In glaucoma, necrotic ganglion cells can reliably be found histologically only in dogs that have had enucleation within 2 days after the onset of clinical disease. (C) Photomicrograph, of the retina from a dog that had optic nerve trauma and enucleation 2 days later, showing extensive ganglion cell necrosis, which suggests that a wave of ganglion cell necrosis occurs before the clinical onset of glaucoma in dogs.

Lens luxation glaucoma (Fig. 13.16)

- Lens luxation is a risk factor for glaucoma for a variety of reasons, not all of which are understood. Complicating interpretation of lens luxation and glaucoma is the fact that lens luxation often occurs as a consequence of buphthalmos in animals with glaucoma
  - Luxation of the lens into the anterior chamber may lead to pupil-block or obstruction of aqueous flow within the anterior chamber, by either the lens itself, or by anteriorly prolapsed vitreous, and the relationship to the development of glaucoma is quite obvious
  - Luxation or subluxation of the lens in the posterior chamber or into the vitreous is also a risk factor for glaucoma, but the mechanism for secondary glaucoma is not as obvious
    - The loss of zonular ligament tension might tend to close the ciliary cleft
    - Anteriorly prolapsed vitreous may obstruct aqueous outflow
- Lens luxation occurs for a variety of reasons, that are discussed in greater detail in Chapter 10
  - Trauma
  - Secondary to glaucoma with enlargement of the globe (buphthalmos)
  - Cataract
  - Breed-related zonular ligament dysplasia
- Special features of glaucoma secondary to lens luxation:
  - About half of dogs with glaucoma secondary to lens luxation do not exhibit the phenomenon of 'tapetal sparing'.

Neovascular glaucoma (Fig. 13.17)

- A diagnosis of neovascular glaucoma implies that the irido-corneal angle is obstructed by peripheral anterior synechiae resulting from a pre-iridal fibrovascular membrane (see Ch. 9)
  - Neovascular glaucoma occurs secondary to an underlying process which stimulates the formation of the neovascular membrane
    - Retinal ischemia secondary to retinal detachment
    - Intraocular neoplasia
    - Uveitis
    - Trauma.

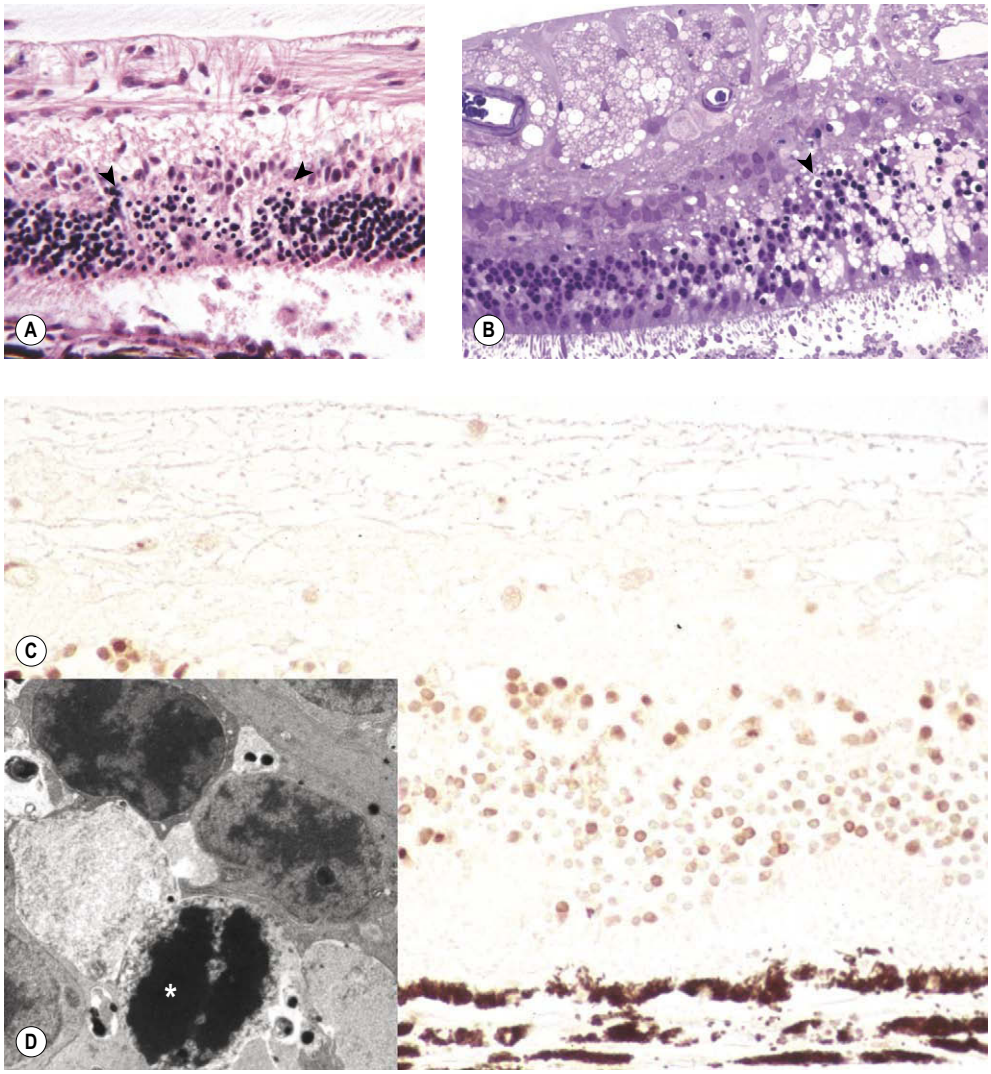


Figure 13.10 Retinal pathology in acute goniodysgenesis glaucoma. (A) Photomicrograph, of the retina from a dog with a 4-day history of glaucoma, showing segmental apoptosis between the arrows. (B) Plastic section, of the retina from a dog with a 4-day history of glaucoma, showing segmental severe edema and apoptosis (arrow) Toluidine blue stain. (C) Photomicrograph showing the retina from a dog with 5-day glaucoma. Numerous apoptotic cells are demonstrated with the TUNEL method brown staining nuclei (D) Electron micrograph from the same dog as (B) showing remnants of the nucleus of a photoreceptor cell undergoing apoptosis (*).

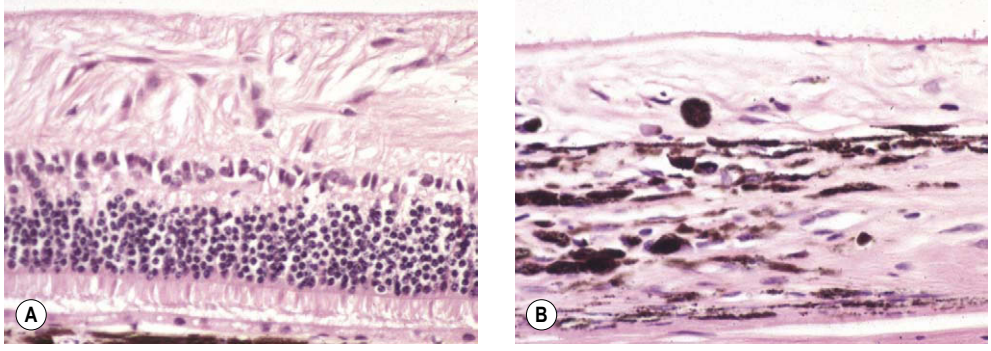


Figure 13.11 Tapetal sparing. (A,B) Photomicrographs, of the central retina from a dog with glaucoma, show the superior or tapetal area (A) and the inferior or non-tapetal area (B). The relative sparing of the superior retina is extreme in this dog, but it is characteristic of most dogs with glaucoma associated with goniodysgenesis.

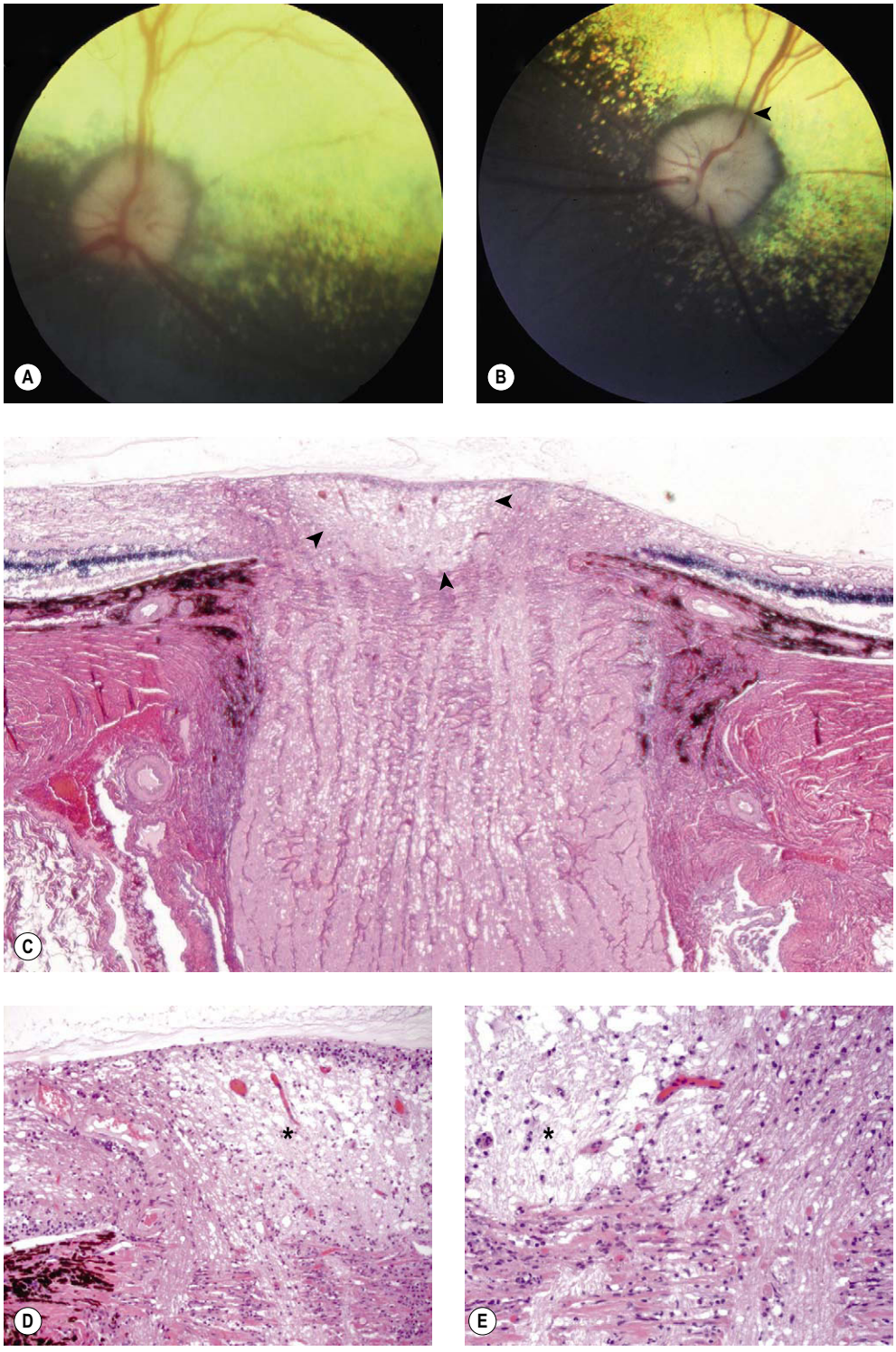


Figure 13.12 Optic nerve disease in acute goniodysgenesis glaucoma. (A) Cocker Spaniel, 8 years old: this is the same image as Figure 13.7(C). The optic disc is swollen and has indistinct margins. (B) This is the same eye as (A), 4 weeks later. The optic disc is slightly pale and depressed as judged by the bend in the retinal vessels (arrow). The eye was visual. (C) Low magnification photomicrograph showing the optic disc and optic nerve from a dog with a 2-day history of glaucoma associated with goniodysgenesis. There is no cupping, but rather swelling and necrotic neuropil in the pale staining area (arrows). (D,E) Higher magnifications showing the necrotic optic disc tissues from the same image as (C) (*).

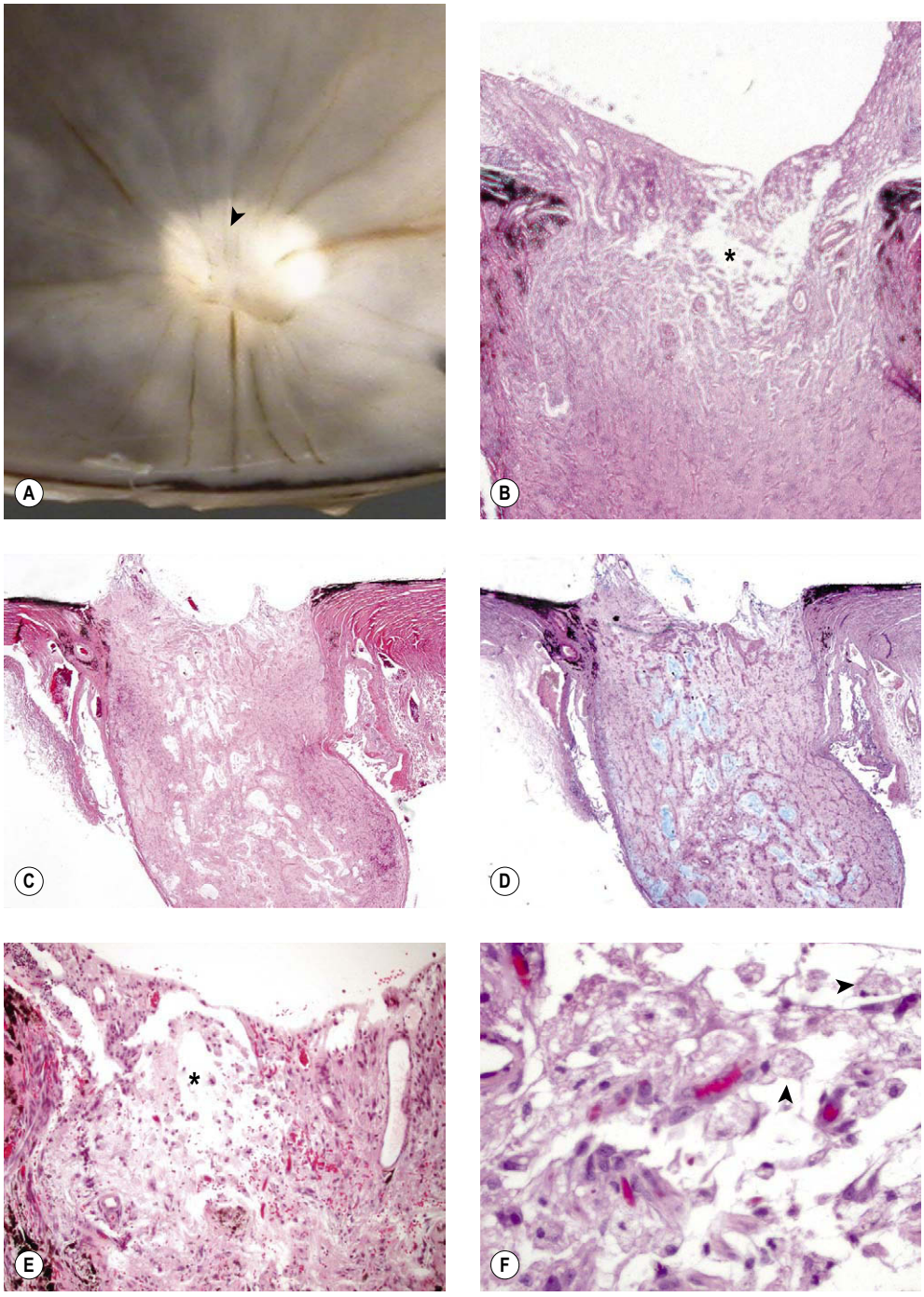


Figure 13.13 Optic nerve pathology in acute goniodysgenesis glaucoma. (A) Gross photograph of a glutaraldehyde-fixed canine globe showing the optic disc from a dog with a 5-day history of glaucoma. Softening and early cupping of the disc neuropil (arrow) and coalescing areas of retinal translucency are seen. (B) Low magnification photomicrograph showing cavitation of the optic disc neuropil (*) after necrotic tissue is removed by phagocytosis. (C,D) Low magnification photomicrographs of a dog retina and optic nerve with a similar history to (A). In (C), H&E showing cavitated tissue extending a long distance from the vitreous surface. In (D), Alcian blue-positive vitreous material pushes deeply into the nerve tissue. Vitreous material occupies the cavitated areas (Alcian blue stain). This phenomenon is called Schnabel's cavernous atrophy. (E,F) Higher magnifications of cavitated area in the neuropil (*) and macrophage cells or gitter cells (arrows).

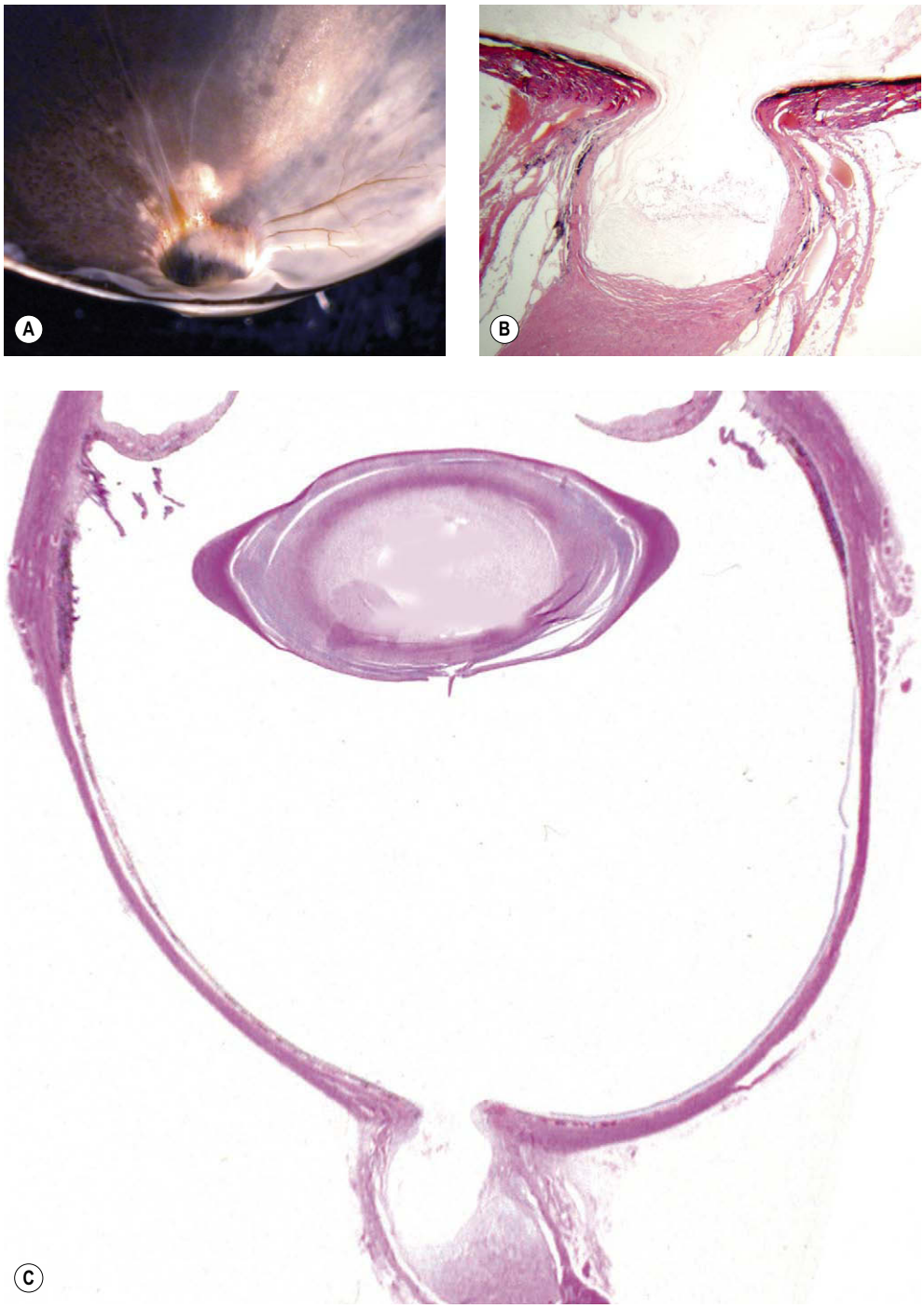


Figure 13.14 Optic nerve pathology in chronic goniodysgenesis glaucoma. (A) Gross photograph showing a deeply cupped optic nerve from a dog with chronic glaucoma. (B) Low magnification photomicrograph showing a deep optic nerve cup, as is often seen in chronic canine glaucoma. (C) Subgross photomicrograph showing an optic nerve head similar to (B).

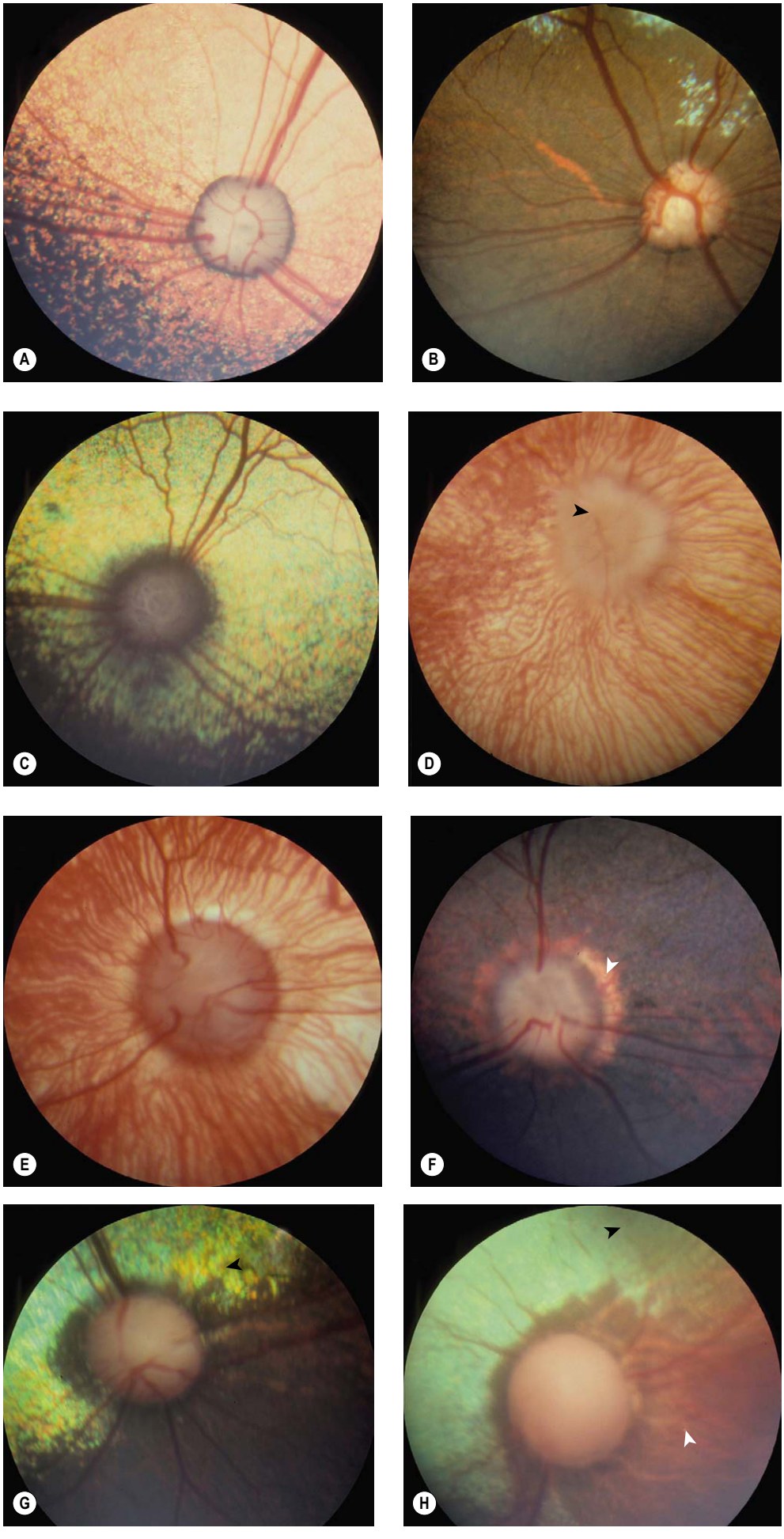


Figure 13.15 Canine optic disc changes in glaucoma, funduscopy. All cases have confirmed glaucoma with various intraocular pressures and durations. (A) Miniature Poodle, 5 years old: the retinal vessels drop over the edge of the cupped disc. (B) Fox Terrier, 4 years old: the optic disc is severely atrophic with a sieve-like appearance of the optic nerve representing the lamina cribrosa. Despite the optic disc atrophy, the retinal vessels appear within normal limits. (C) Mixed Breed, 7 years old: the optic disc has a prominent sieve-like appearance of the optic nerve representing the lamina cribrosa which is visible because there has been a loss of myelin. (D) Siberian Husky, 4.5 years old: Retinal vessels are difficult to discern in this subalbinotic atapetal fundus. The optic disc within the myelin sheath is depressed (arrow). (E) Siberian Husky, 6 years old: the retinal vessels are easily discernible. The optic disc is pale and cupped 360°. (F) Mixed Breed, 1.5 years old: this disc is pale and cupped, especially in the superior half. Choroidal vessels and sclera (arrow) are present peripapillary due to the retinal atrophy in this atapetal fundus. (G) Samoyed, 6 years old: the optic disc is pale and cupped 360°. Tapetal hyperreflectivity (arrow) and peripapillary pigmentation indicate retinal atrophy. (H) Samoyed, 5 years old: severe cupping prevents visualizing any optic disc structure. Tapetal hyperreflectivity was present superiorly (black arrow) depending on the light incidence. Choroidal vessels are present at the white arrow.

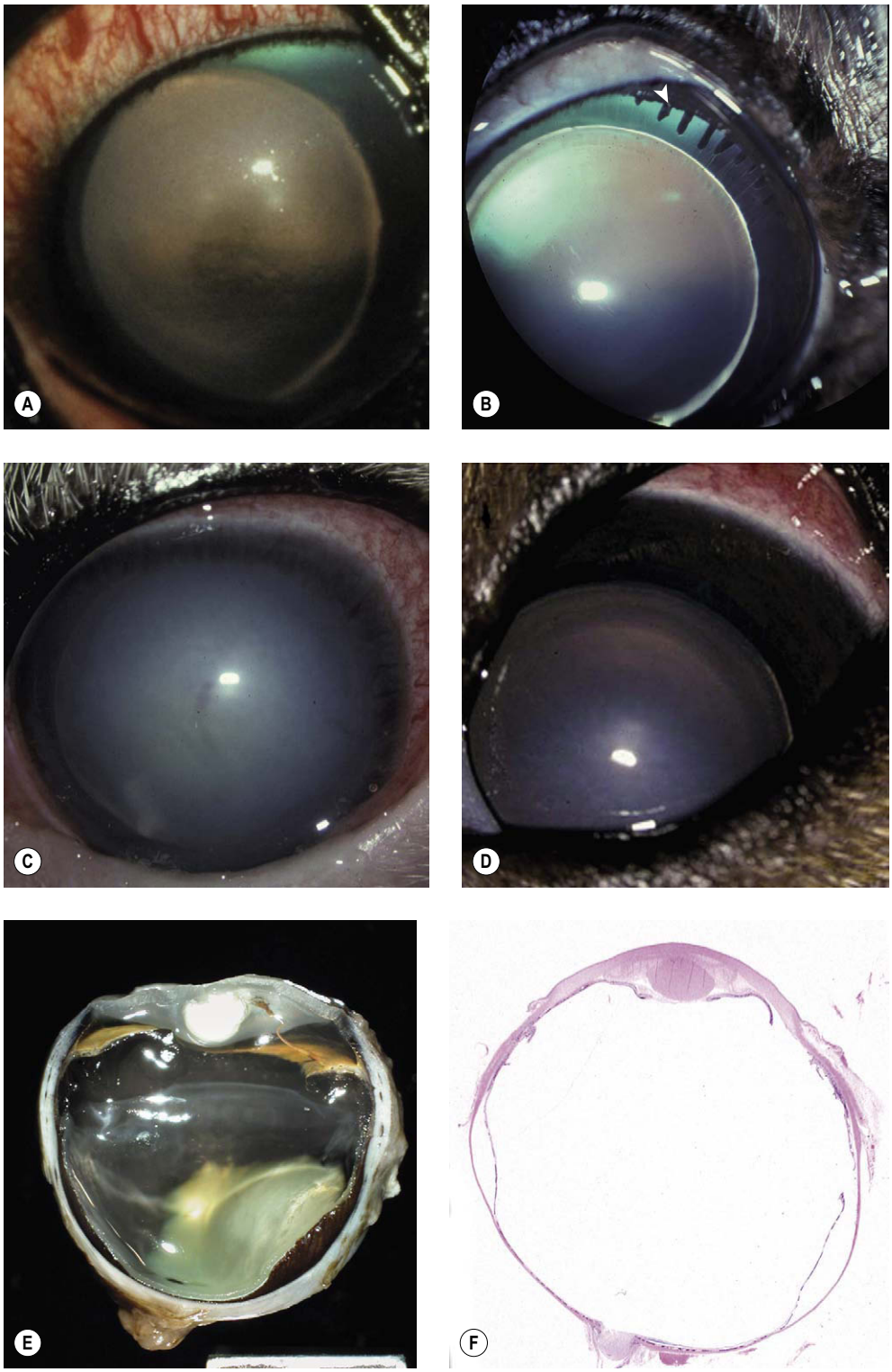
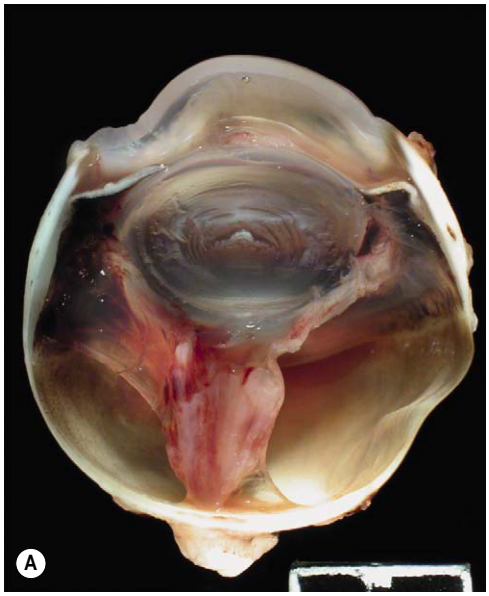
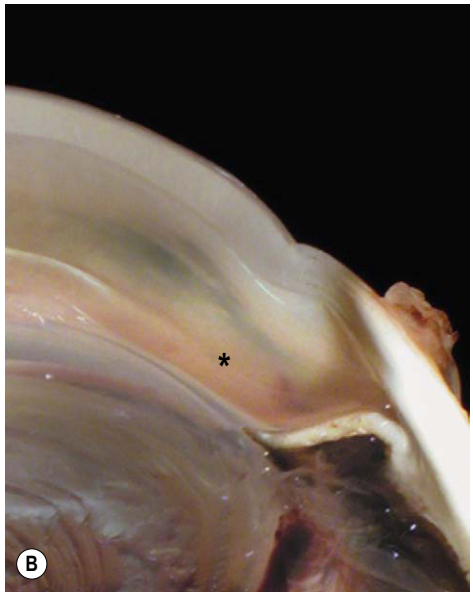
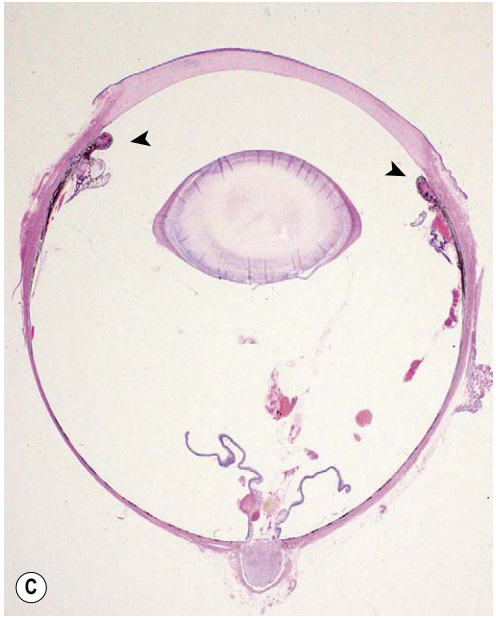
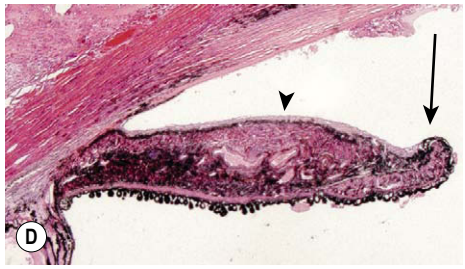


Figure 13.16 Lens luxation glaucoma. (A) Dandie Dinmont Terrier, 5 years old: the lens is subluxated posteriorly and temporally resulting in a nasal aphakic crescent. (B) Sealyham Terrier, 6 years old: the majority of the lens equator can be visualized. Ciliary processes (arrow) can be seen nasally with their zonular fibers. (C) Boston Terrier, 9 years old: the lens has totally luxated into the anterior chamber. The lens equator is difficult to see due to corneal edema. (D) Parson Russell Terrier, 5 years old: the entire lens is luxated into the anterior chamber. There is regional corneal edema secondary to lens contact with the corneal endothelium. (E,F) Gross and subgross photomicrographs showing canine globes with lens luxation into the anterior chamber. The lens is entrapped in the anterior chamber obstructing aqueous drainage.









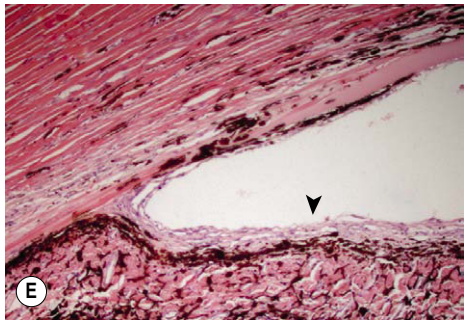


Figure 13.17 Neovascular glaucoma. (A) Gross photograph of a canine globe with retinal detachment, pre-iridal fibrovascular membrane and peripheral anterior synechia. (B) Magnified view of the same globe showing the pre-iridal fibrovascular membrane on the iris surface and extending across the angle (*). (C) Subgross photomicrograph, from a Shih Tzu with retinal detachment associated with vitreoretinopathy, showing a distorted iris profile (arrows) because of pre-iridal fibrovascular membrane and ectropion uvea. (D) Low magnification photomicrograph, of the iris from a dog with neovascular glaucoma, showing a pre-iridal fibrovascular membrane (arrowhead) and mild ectropion uvea (arrow). (E) Higher magnification of the image in (D) showing the peripheral anterior synechia (arrow).

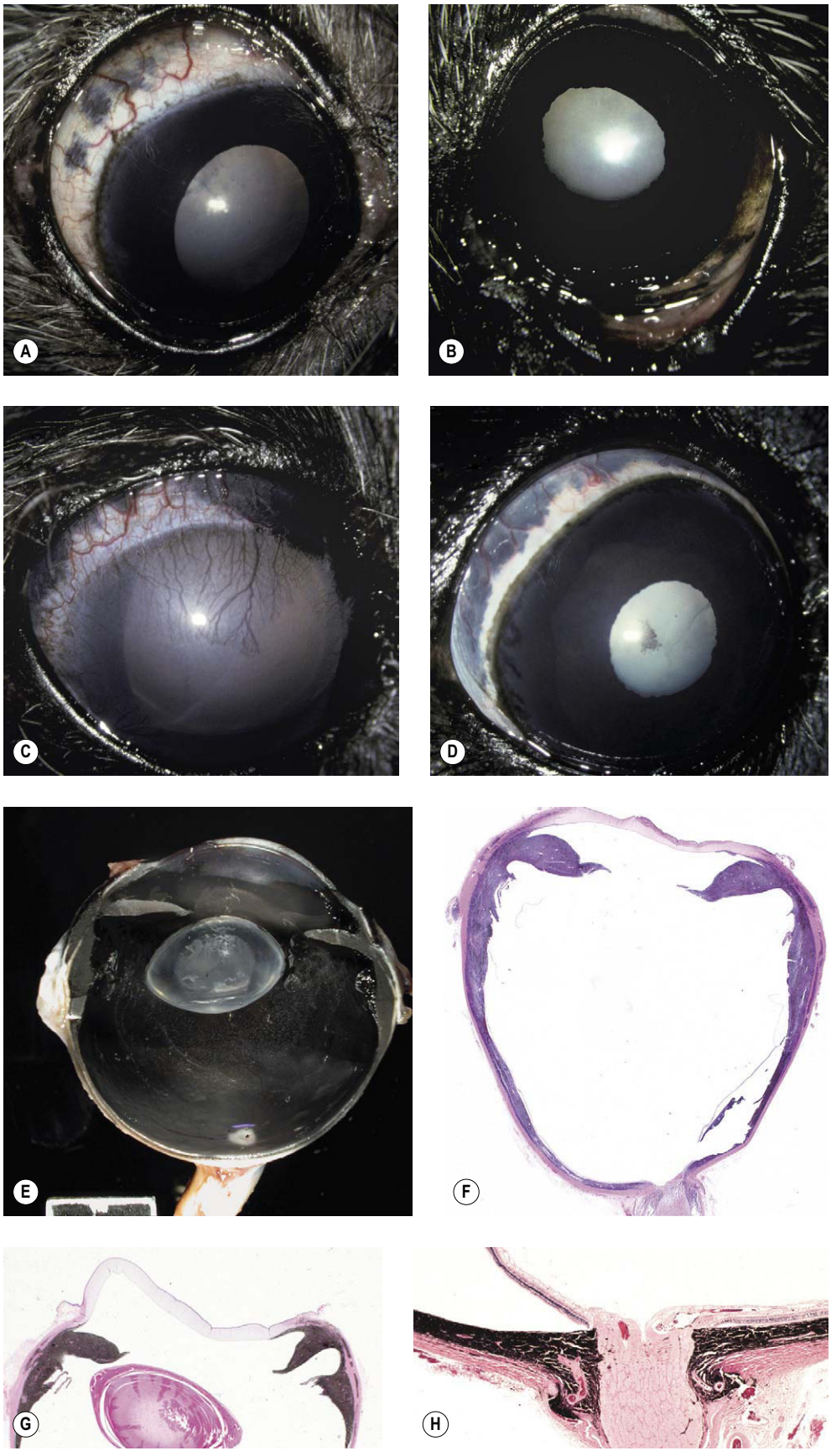
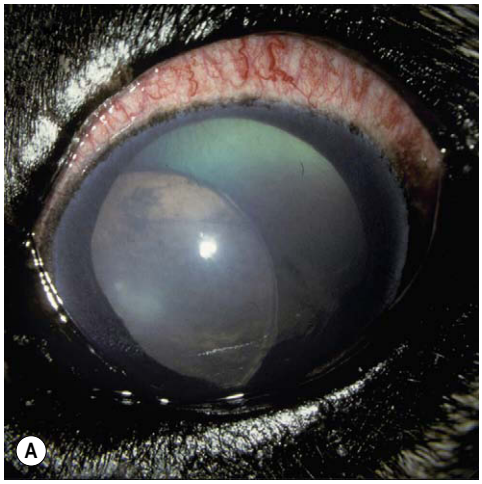


Figure 13.18 Glaucoma associated with ocular melanosis in the Cairn Terrier. (A) Cairn Terrier, 13 years old: scleral pigment and a darkly pigmented iris were present. (B) Cairn Terrier, 12 years old: the heavily pigmented iris resulted in dyscoria and an areflexic pupil. (C) Cairn Terrier, 9 years old: the sclera is heavily pigmented, as is the iris. Descemet's streaks (Haab's stria) and corneal vascularization are also present. (D) Cairn Terrier, 13 years old: diffuse scleral pigment is present. Heavy iris pigment resulted in a small pupil that did not dilate. The iris pigmentation is most prominent at the iris base. Pigment is also present on the anterior lens. (E) Gross photograph showing the globe from a Cairn Terrier with glaucoma associated with ocular melanosis. The excessive pigmentation thickens and distorts the iris and also the posterior uvea. (F) Subgross photomicrograph, from an affected Cairn Terrier, showing a diffusely hyperpigmented uvea and distortion of the iris base, anterior ciliary body and the limbal scleral tissues. (G) Subgross photomicrographs from an affected Cairn Terrier. The iris base, anterior ciliary body and limbus are affected to the point where they have lost their structural integrity. (H) Examination with low power magnification of the choroid and tissues around the optic nerve is useful in determining whether there is excessive pigment.



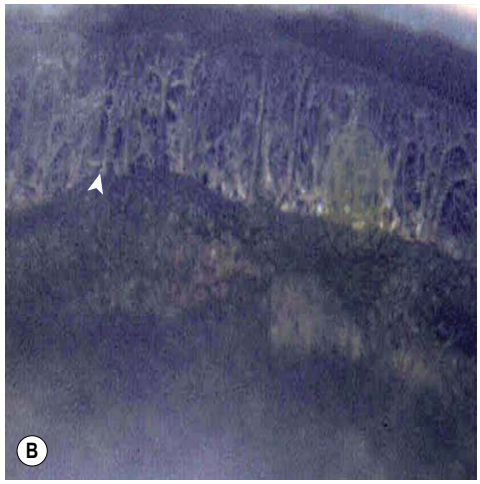


Figure 13.19 Ocular melanosis in breeds other than the Cairn Terrier. (A) Boxer, 9 years old: the iris is poorly visualized due to corneal edema and pupil dilation, but it is heavily pigmented. The lens is luxated posteriorly and temporally secondary to glaucoma. (B) Scottish Terrier, 13 years old: this is a close-up of the irido-corneal angle, showing the darkly pigmented iris. The thickened, pigmented pectinate ligaments extend from the base of the iris (arrow) to their corneal insertion. The ciliary cleft is also heavily pigmented.

Glaucoma in canine ocular melanosis (Figs 13.18, 13.19)

- Obstruction of aqueous outflow at the level of the irido-corneal angle and ciliary cleft occurs as a frequent complication in dogs with primary ocular melanosis, or so-called 'pigmentary glaucoma'
- Ocular melanosis is diagnosed when the uveal tract is thickened and distorted by an excess of heavily pigmented tissue (see Ch. 9)
- Ocular melanosis is often associated with secondary glaucoma
- Breeds with the highest incidence are:
  - Cairn terrier ('pigmentary glaucoma')
    - The most commonly affected breed, in which the disease has been most extensively studied
    - Affected dogs usually show bilateral ocular involvement
    - A dominant mode of inheritance has been proposed in this breed
  - Labrador Retriever
  - Boxer
  - Dachshund
- There is a small, but documented risk of melanoma developing in eyes with ocular melanosis.

Multiple thin-walled iridociliary cysts, pigmentary uveitis in Golden Retrievers (Fig. 13.20) (see also Ch. 9)

- Although also documented in the Great Dane, thin-walled iridociliary cysts associated with glaucoma are rarely seen in breeds other than the Golden Retriever
- One-cell-thick cysts of ciliary or iridal epithelial origin fill the posterior chamber and become plastered against the lens equator or the anterior capsule. The cyst can pull the iris back to form a posterior synechia
- The disease is called 'pigmentary uveitis' by ophthalmologists because of the protein in the aqueous, the dispersion of pigmented cells and fragments of cysts, and because pigmented cyst remnants are plastered against the anterior lens capsule mimicking inflammatory posterior synechiae or 'iris rests'
- Morphologically, inflammation is a minor process in affected globes
- Focal retro-corneal membrane or Descemet's changes are seen because fragments of cysts attach to the corneal endothelium
- The precise mechanism for glaucoma development in affected dogs is unclear:
  - Multiple cysts within the posterior chamber can push the iris anteriorly, narrowing the opening to the ciliary cleft
  - Posterior synechiae or iris bombé are frequently seen in globes removed because of secondary glaucoma
  - Pre-iridal fibrovascular membranes are commonly encountered, often with concurrent peripheral anterior synechiae
  - Intraocular hemorrhage is common.

Glaucoma associated with neoplasia in dogs

- Of 5722 cases of neoplasia in dogs in the COPLOW collection, 1516 cases (26%) have glaucoma as part of the syndrome
  - 57% melanoma
  - 21% iridociliary epithelial tumors
  - 5% metastatic tumors
  - 4.5% lymphoma.

Comparative Comments

Secondary open-angle glaucoma refers to a group of diseases characterized by elevated intraocular pressure occurring with a well-formed anterior chamber without peripheral anterior synechiae. There are a number of types of secondary open-angle glaucoma recognized in humans:

- Inflammatory disorders may cause a trabeculitis or may result in mechanical blockage of aqueous outflow by proteinaceous exudates
- The presence of blood products may produce open-angle glaucoma in several ways
  - Red blood cells from hemophthalmos, or macrophages containing degenerated blood cells, may block aqueous outflow
  - In the case of a vitreous hemorrhage, red blood cells are lysed progressively and the rigid degenerating cells ('ghost cells') may migrate into the anterior chamber and obstruct the trabecular spaces

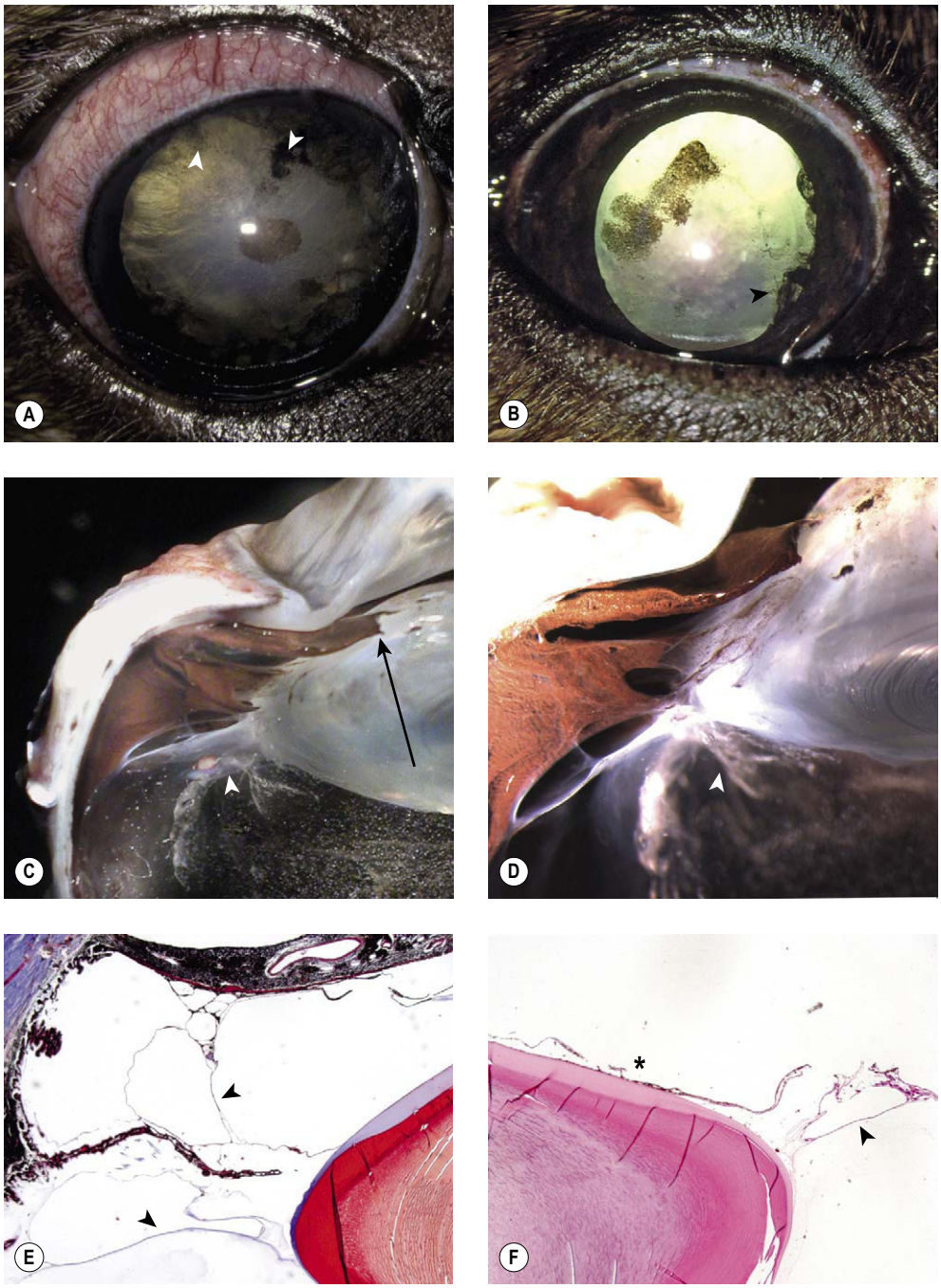


Figure 13.20 Thin-walled iridociliary cysts (pigmentary uveitis) in the Golden Retriever. (A) Golden Retriever, 7 years old: pigment can be seen on the axial anterior lens and near the pupil margin (arrows). (B) Golden Retriever, 9 years old: the iris is darkly pigmented. Ruptured iris cysts are present at the pupil margin (arrow). The pigment to the left is on the anterior lens capsule. (C,D) Magnified gross photographs of the posterior chamber, anterior vitreous face and lens equator, from two Golden Retrievers, show the translucent cyst remnants (arrowheads) and pigmented cyst remnants on the lens capsule, as well as synechia (arrow). (E,F) Low magnification photomicrographs show thin-walled cysts and cyst remnants spanning the posterior chamber (arrows) and adherent to the lens capsule (*). The epithelial cells of the cysts can be pigmented or non-pigmented.

Comparative Comments (continued)

  - Liquefied cortex may leak from the lens and lead to an influx of swollen mononuclear cells, which may obstruct the outflow system (phacolytic glaucoma). Liquefaction of the lens cortex may also lead to the release of particulate material into the anterior chamber, which itself can block the trabecular meshwork
- In some patients, a dispersion of pigment from the iris pigmented epithelium may occur. Phagocytosis of melanosomes by the trabecular endothelial cells may lead to obstruction of aqueous outflow and glaucoma (pigmentary glaucoma)
- The pseudoexfoliation syndrome is a systemic disorder in which there is a deposition of a fibrillary protein-like material on the lens capsule, zonular fibers, trabecular meshwork, iris, ciliary body, and other ocular structures, as well as in other connective tissues
  - Between 10% and 23% of patients with pseudoexfoliation syndrome develop glaucoma
  - The trabecular meshwork in pseudoexfoliation syndrome also contains an excessive amount of pigment
- Siderosis, from retained ocular foreign bodies, can cause open-angle glaucoma
- Blunt trauma to the ocular anterior segment can damage the trabecular meshwork and the base of the iris, and produce subsequent scarring in the trabecular meshwork or posterior proliferation of the peripheral corneal endothelium over the angle structures. This can lead to increased intraocular pressure and the development of glaucoma
- Additional forms of secondary open-angle glaucoma are anterior chamber epithelialization and anterior chamber endothelialization

Secondary angle-closure glaucoma is seen in four circumstances in human eyes:

- Neovascular glaucoma
  - Enucleated eyes with neovascular glaucoma are commonly seen in human eye pathology laboratories. Neovascular membranes occur as a complication of diabetic retinopathy, central retinal vein occlusion, intraocular neoplasia, and long-standing retinal detachment. A common feature in all of these is the formation of angiogenic factors acting on the iris vessels. New vessel production and subsequent contraction of the fibroblastic component of the membrane can draw the iris pigment epithelium through the pupil onto the front of the iris, as well as causing peripheral anterior synechiae and angle closure
- Tumors
  - In secondary angle-closure glaucoma due to tumor, there is mechanical displacement of the iris and lens by tumors of the ciliary body, choroid, or retina, which leads to pupillary blockage
- Uveitis
  - In cases of uveitis, the sticky fibrinous exudate is responsible for the formation of peripheral anterior and central posterior synechiae, which cause secondary angle closure and glaucoma. With severe or prolonged inflammation, neovascularization will also contribute to the rise in intraocular pressure
- Trauma
  - Following surgical or nonsurgical trauma, because of perforation of the cornea or limbus, hypotony and reactionary fibrosis may lead to peripheral anterior synechiae compromising the chamber angle.

THE FELINE GLAUCOMAS

Some general features of feline glaucoma compared to canine glaucoma

- Glaucoma is relatively uncommon in the cat compared to the dog, although it is possible that many feline cases go unrecognized. In contrast to the situation in dogs, feline glaucoma is often an insidious, gradually progressive disease. Moderate elevations in IOP are associated with few overt clinical signs and cats are frequently not presented for evaluation until late in the disease process
- Sudden, fulminant onset of disease is not typical of the feline glaucomas, which makes it difficult to determine the progressive steps that occur early in the disease process
- In one recent retrospective study, 73% of glaucomatous cats were blind at the time of initial presentation. However, some vision may be preserved in chronically glaucomatous cats despite gross buphthalmos
- The optic nerve is often more gliotic and atrophic, rather than necrotic
- There is typically a loss of retinal ganglion cells but the outer retina does not progressively degenerate unless there are other factors in play, such as trauma.

The majority of cases of feline glaucoma are secondary to other ocular disease

- Intraocular inflammation, particularly chronic lymphoplasmacytic uveitis (see below), is a frequently reported cause of glaucoma in cats and may lead to elevation of IOP through a number of different pathogenic mechanisms
- Intraocular hemorrhage, particularly related to high blood pressure in elderly cats may also result in secondary glaucoma
- Intraocular neoplasia is another important cause of glaucoma in cats
- Lens-associated glaucoma in cats
  - May occur secondary to phacoclastic uveitis resulting from lens trauma
  - In contrast to dogs, lens luxation in cats is often secondary to glaucoma or uveitis and seldom directly results in glaucoma.

Lymphoplasmacytic uveitis (Fig. 13.21)

- Lymphoplasmacytic uveitis is one of the most common causes of feline glaucoma, and is second to diffuse iris melanoma as the most common cause of feline glaucoma resulting in enucleation. Of the total number of feline submissions to COPLOW, 10% are lymphoplasmacytic uveitis with glaucoma
- Globes submitted to the pathology lab are enucleated because of vision loss and blindness due to glaucoma
- While lymphoplasmacytic uveitis does not invariably lead to glaucoma, globes with concurrent glaucoma are more likely to be submitted for histopathologic evaluation
- This is an idiopathic uveitis characterized by a lymphoplasmacytic infiltrate in the iris and ciliary body
  - The formation of lymphoid follicles is a distinctive feature commonly seen in affected globes
- Other morphologic features often seen in feline lymphoplasmacytic uveitis are described in Chapter 9
- Pathogenesis of glaucoma in feline lymphoplasmacytic uveitis

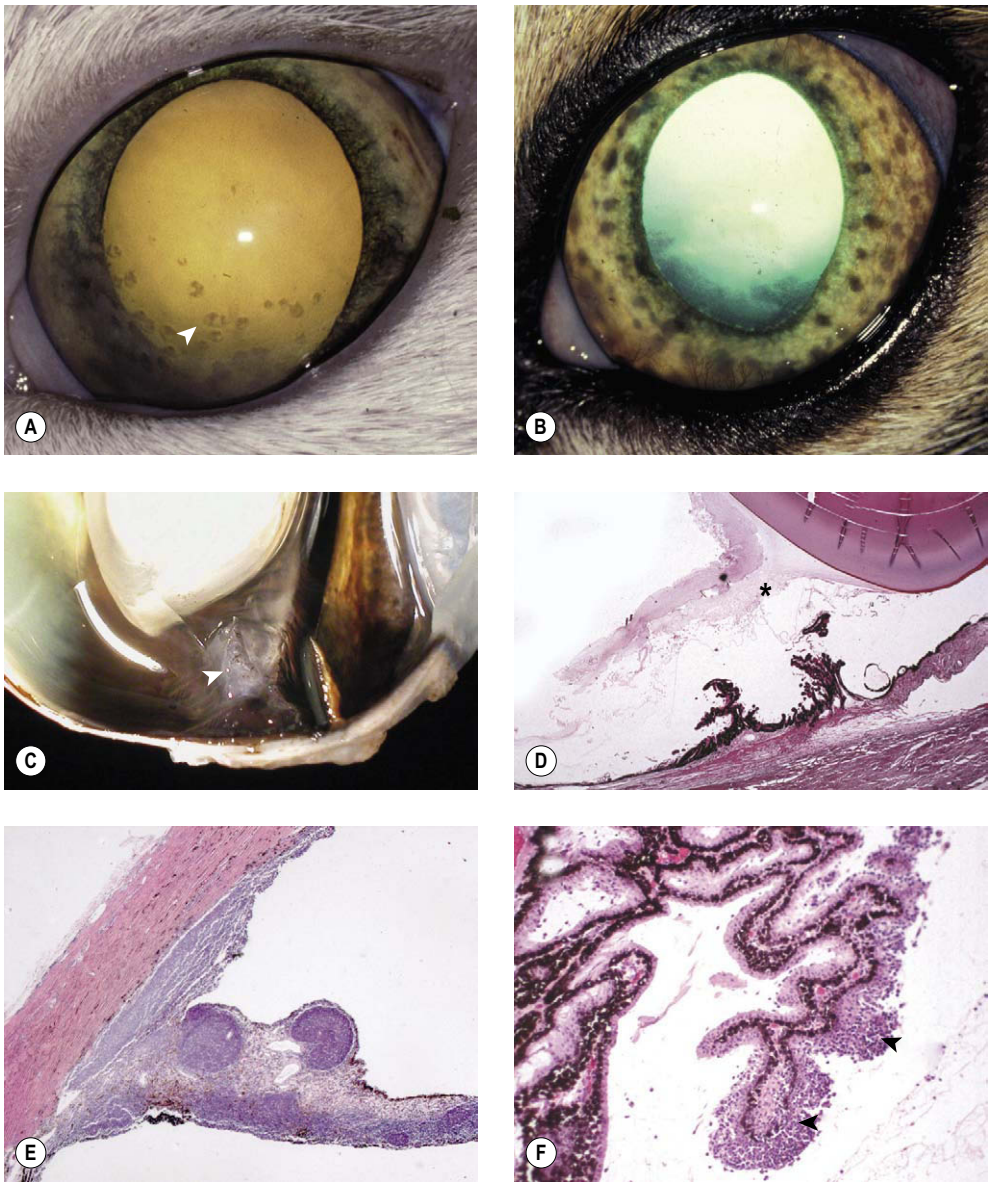


Figure 13.21 Glaucoma associated with lymphoplasmacytic uveitis in cats. (A) DSH, 6 years old: the iris was inflamed. Keratitic precipitates (arrow) are present inferiorly. Etiology was based on a positive *Bartonella* serology. (B) DSH, 5 years old: multiple dark foci of inflammation are present. Etiology was based on a positive *Toxoplasma* serology. (C) Magnified gross photograph of an affected feline globe showing condensed vitreous material in the posterior chamber (arrow). (D) Low magnification photomicrograph of another affected cat eye showing condensed protein-rich vitreous material prolapsed into the posterior chamber (*). (E) Photomicrograph of an affected cat eye showing the iris and irido-corneal angle. There is an intense lymphoplasmacytic cellular infiltrate, including two lymphoid follicles. This is a characteristic disease feature, which appears in some, but not all, cats. (F) Photomicrograph showing the pars plicata of an affected cat. Inflammatory cells are entrapped directly within the ciliary epithelial layer (arrows). This is a common feature of both inflammation and lymphoma in the eye. It is not a specific feature of feline lymphoplasmacytic uveitis.

- The most frequently cited mechanism is the inflammatory infiltration with obliteration of the aqueous outflow structures
  - In many affected globes, the extent of the inflammatory infiltrate within the irido-corneal angle and ciliary cleft is minimal, and these drainage angle structures remain intact
- Other factors that might contribute to the pathogenesis of glaucoma in lymphoplasmacytic uveitis include:
  - Lens luxation
  - Vitreous prolapse
  - Neovascular membranes (rarely seen)
  - Synechiae.

Glaucoma associated with feline diffuse iris melanoma (Figs 13.22, 13.23)

- In the COPLOW collection, this appears to be over-represented relative to clinical incidence of the syndrome. Of the total feline submissions, 53% have neoplasia. 11% are diagnosed as melanoma with glaucoma. Of the total feline submissions, 26% have feline diffuse iris melanoma (see also Ch. 9).

Aqueous humor misdirection syndrome (malignant glaucoma) (Fig. 13.24)

Unlike melanoma, this syndrome is vastly under-represented in the COPLOW collection. There are a total of 10 cases in the COPLOW collection.

- Although loss of vision is common, these eyes are not characteristically red or painful
- The disease has an insidious onset in older cats.

Clinical features of aqueous humor misdirection syndrome

- Dilation of the pupil with associated anisocoria, as the disease is frequently unilateral at the time of initial presentation

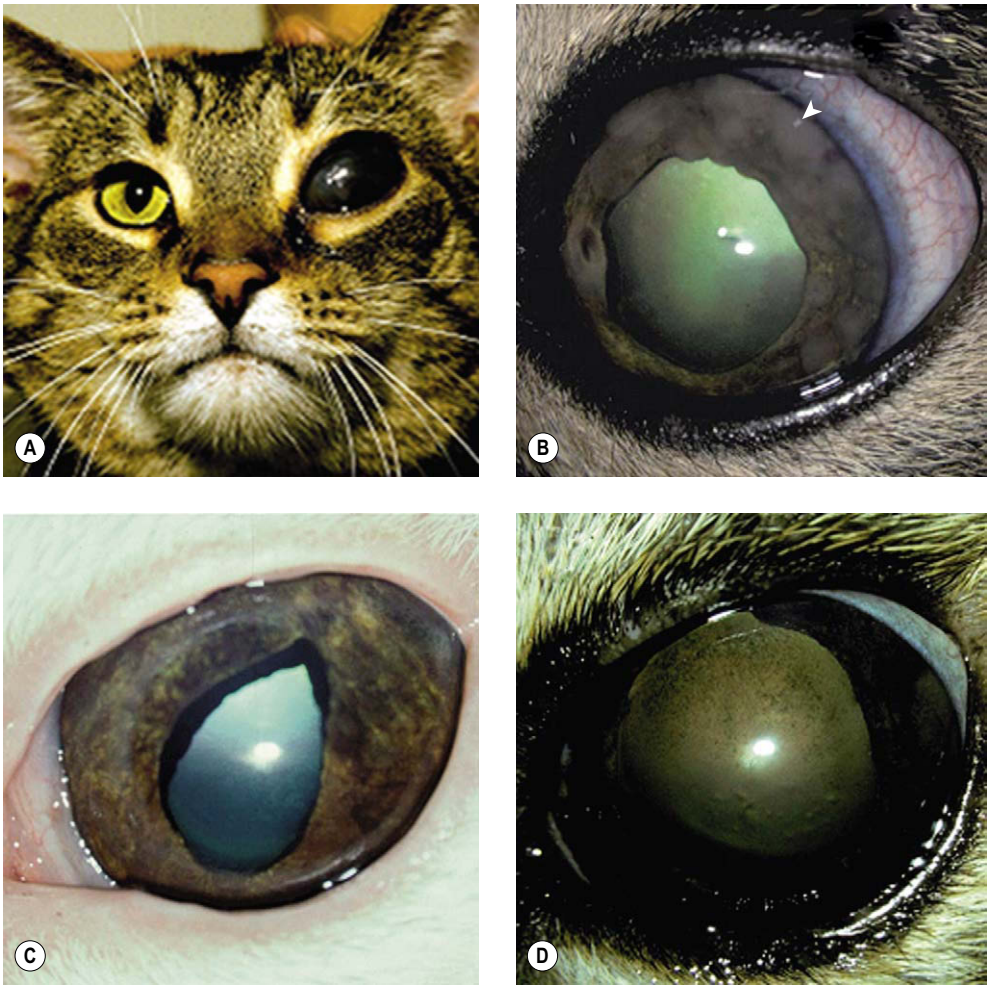


Figure 13.22 Glaucoma associated with feline diffuse iris melanoma, clinical. (A) DSH, 6 years old: Chronic glaucoma resulted in a buphthalmic globe. Iris detail cannot be seen in this photograph. (B) DSH, 9 years old: the iris is irregularly thickened with pale elevated masses (arrow). (C) DSH, 13 years old: the iris is heavily pigmented, resulting in dyscoria. Ectropion uvea or neoplastic infiltrate accounts for the dark area along the pupil margin. (D) DSH, 14 years old: the iris is heavily pigmented with a ragged pupil margin. Pigmented cells are present on the anterior lens capsule.

- Uniformly shallow anterior chamber associated with anterior displacement of the iris and lens
- Decreased pupillary light reflex
- Decreased menace response
- Subtle, glaucomatous abnormalities of the optic nerve head
- Ocular ultrasonography reveals thickening of the anterior vitreous face, anterior displacement of the iris and lens, and clear spaces in the vitreous cavity.

Morphologic features of the aqueous misdirection syndrome

- These globes are very quiet and the changes are easily missed
- Grossly the vitreous may be partially liquid, or irregular in viscosity
- The anterior face of the vitreous is thickened because of excess mucinous deposition with or without a spindle cell component
- The anterior vitreous is pushed forward, crowding into the posterior chamber, yet the anterior face of the vitreous remains well defined
- The changes seen in the optic nerve and retina are as expected with other kinds of glaucoma in cats

It has been postulated that aqueous humor is misdirected posteriorly, becoming trapped within 'pools' in the vitreous cavity

- Subsequently, anteriorly displaced vitreal elements become condensed, compressed and juxtaposed against the lens and ciliary processes.
- This juxtaposition is responsible for so-called 'cilio-vitreal-lenticular block', with elevation in IOP, collapse of the ciliary cleft and narrowing of the irido-corneal angle.

Angle recession (contusion) glaucoma (Fig. 13.25)

- The defining feature of angle recession is the posterior position of the irido-corneal angle
- This change is usually seen in conjunction with lymphoplasmacytic uveitis and there is seldom a history of trauma
- The existence of a distinct entity of angle recession glaucoma in cats (and more rarely in dogs) is subject to debate for the following reasons:
  - The structures of the normal feline irido-corneal angle are widely spaced, and clearly defined criteria that indicate pathologic angle recession are lacking
  - This change is usually seen in eyes with concurrent lymphoplasmacytic uveitis, which can be responsible for glaucoma independent of the presence of angle recession

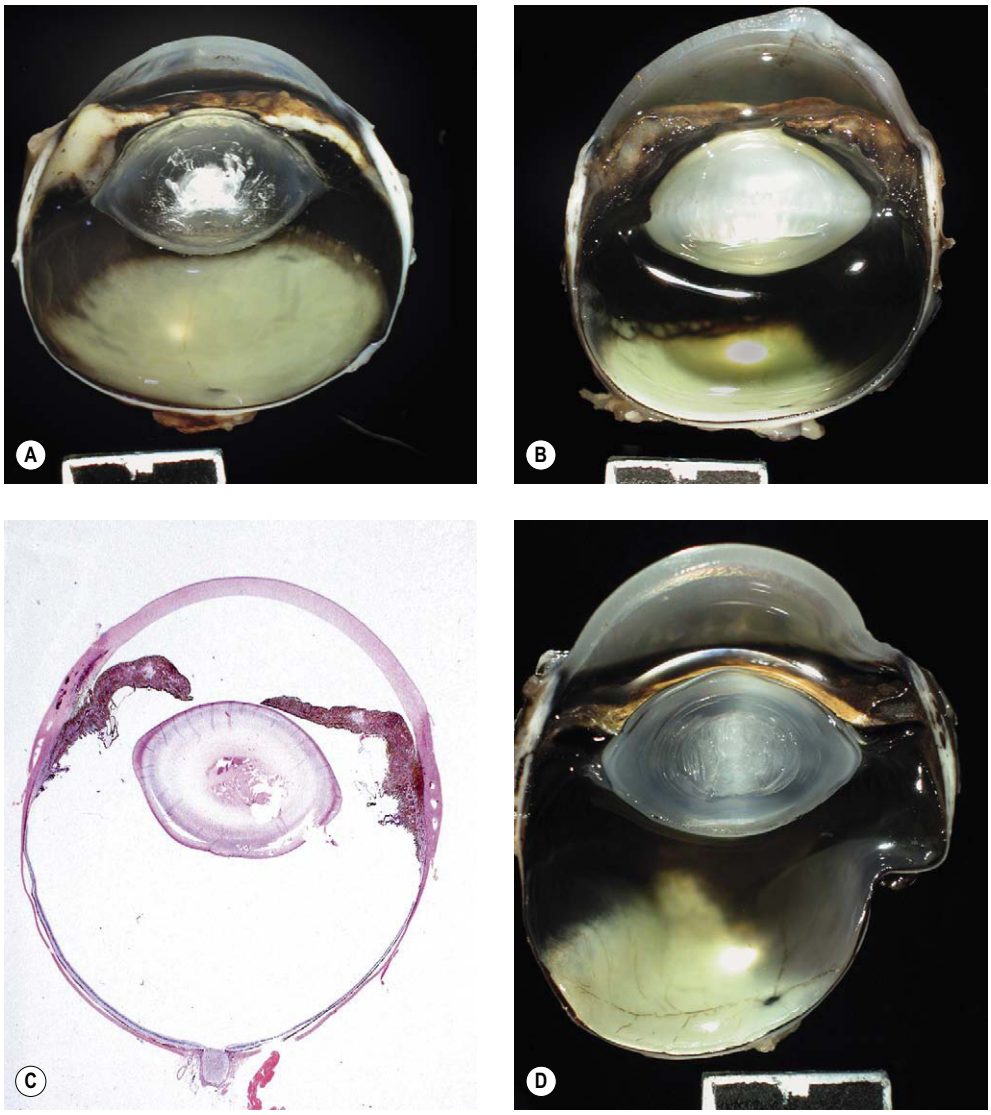


Figure 13.23 Glaucoma associated with feline diffuse iris melanoma, pathology. (A–D) Gross and subgross images show cat eyes with feline diffuse iris melanoma and secondary glaucoma.

  - If, as is the case for the human disease, glaucoma does not develop until years after the traumatic incident, it is unlikely that this incident will be reported in the history
- The proposed pathogenesis of angle recession
  - Blunt force trauma deforms the globe, pushing the cornea anteriorly
  - This sets off a rapid rebound of the lens, pulling on the ciliary body causing cyclodialysis

Morphologic features which support the significance of angle recession as a factor in the pathogenesis of some feline glaucomas

- The feline irido-corneal angle is very delicate and the individual pillars of the pectinate ligament are small in diameter and, for that reason, probably more susceptible to rupture during trauma
- Feline globes with a history of trauma often show cyclodialysis if removed early after the event, or angle recession if removed long after the event
- Affected globes often have other features that could reflect previous trauma such as:
  - Cataract
  - Lens capsule rupture
  - Segmental, full thickness, retinal degeneration not otherwise expected in feline glaucoma

Spontaneous primary glaucoma is relatively rare in the cat

Both open-angle glaucoma, and glaucoma associated with pectinate ligament dysplasia, have been reported in adult cats. Breeds that may be at increased risk of primary glaucoma include the Siamese, Burmese and Persian. There are 11 feline globes in the COPLOW collection with glaucoma and a completely open and normal-appearing irido-corneal angle, with no abnormalities seen in the ciliary cleft or the corneoscleral trabecular meshwork

- Feline open-angle glaucoma (Fig. 13.26)
  - These are consistently unilateral
  - There are clearly evident glaucomatous changes in the retina and optic nerve head
  - The Burmese breed is over represented
  - There is often a subtle myxomatous change in the stroma immediately around the vortex veins in the sclera

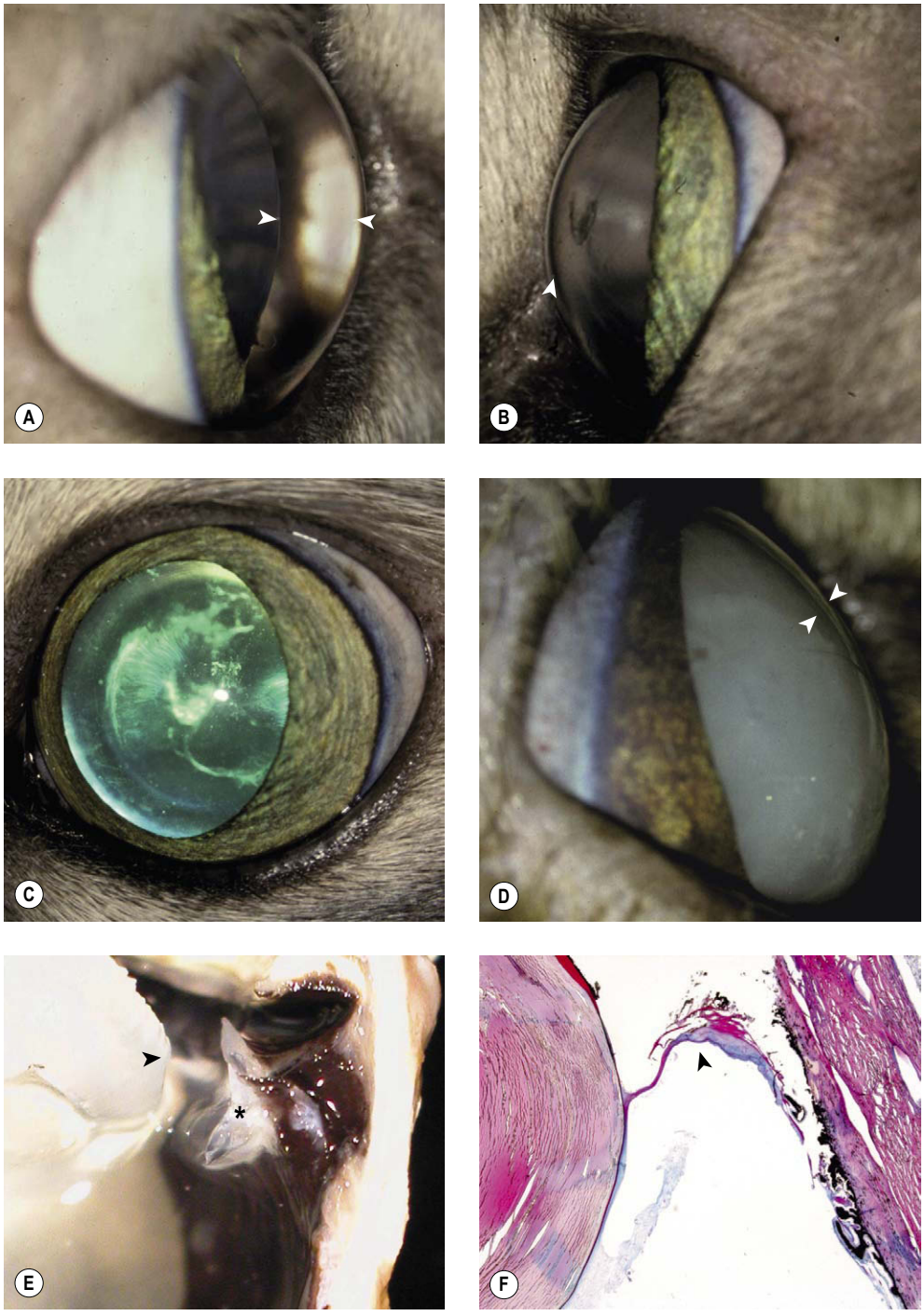


Figure 13.24 Feline aqueous humor misdirection syndrome (FAHMS). (A) DSH, 12 years old: this is a profile of the right eye. The iris is slightly displaced anteriorly. The anterior chamber between the cornea (right arrow) and lens (left arrow) is shallow. (B) This is the left eye of the cat in (A). The lens and iris are displaced so anteriorly that only a small dark line represents the anterior chamber (arrow). (C) DSH, 11 years old: the iris and lens were displaced anteriorly. A diffuse anterior cortical cataract is also present. (D) DSH, 14 years old: the white arrow points to the cornea and the black arrow to the anterior surface of the mature cataract. The anterior movement of the iris and lens has greatly reduced the anterior chamber. (E) Gross photograph of the anterior vitreous and the lens equator (arrow) showing the forward bowing of the vitreous and the solidified anterior vitreous face (*). (F) Low magnification photomicrograph showing the anterior vitreous face, which is bowing forward (arrow). The solidified anterior vitreous face has both an Alcian blue component (proteoglycans) and a PAS component. While not visible in this slide, usually, there are also spindle cells within the PAS component.

- Feline congenital glaucoma
  - Sporadic cases of feline congenital or early-onset glaucoma associated with ocular malformations, including microphakia, ectopia lentis, iridoschisis, pectinate ligament dysplasia, multiple iridociliary cysts and persistent pupillary membranes have been reported in the veterinary literature
  - A colony derived from Siamese cats with inherited congenital glaucoma has been established and may serve as a valuable model for human disease
- Congenital glaucoma is a form of open-angle glaucoma that arises in children before the age of two. It appears to be the result of abnormal development of the trabecular meshwork
- Among the histopathologic findings described in congenital glaucoma are an abnormal anterior attachment of the iris root to the trabecular meshwork, a poorly developed scleral spur and uveal meshwork, thickening of the beams of the trabecular meshwork, incomplete separation of the angle structures with retained fetal tissue, and an abnormal anterior attachment of the longitudinal fibers of the ciliary muscle to the uveal trabecular meshwork
- Prolonged elevated intraocular pressure in infants and young children may cause enlargement of the globe (buphthalmos), as the sclera expands and thins. Limbal ectasia and an enlarged cornea can occur, with circumferential or horizontal tears of

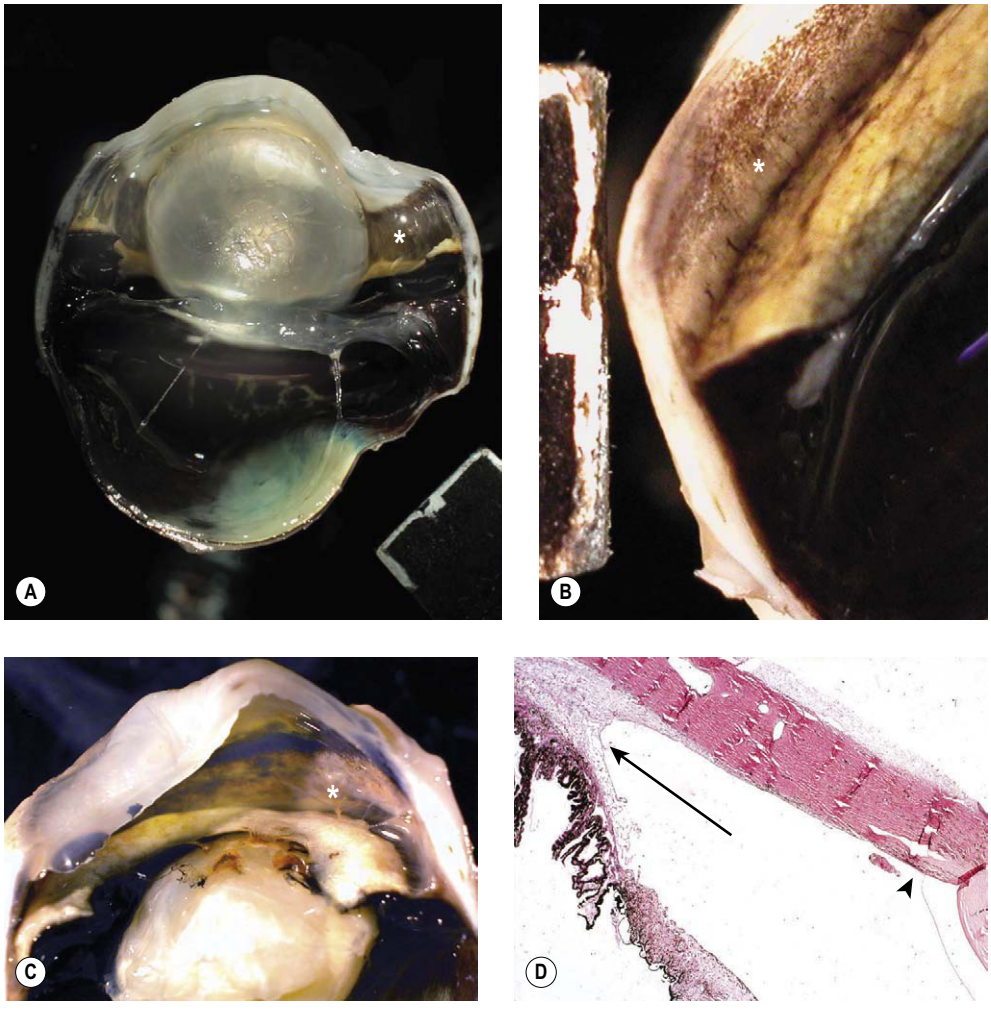


Figure 13.25 Irido-corneal angle recession and glaucoma in cats. (A–C) Gross photographs of feline globes show a wide space between the end of Descemet's membrane and the iris base (*). The cause of this recession of the irido-corneal angle is not known, but it might be secondary to prior cyclodialysis. (D) Low magnification photomicrograph showing the increased distance between the end of Descemet's membrane (arrowhead) and the iris base (arrow).

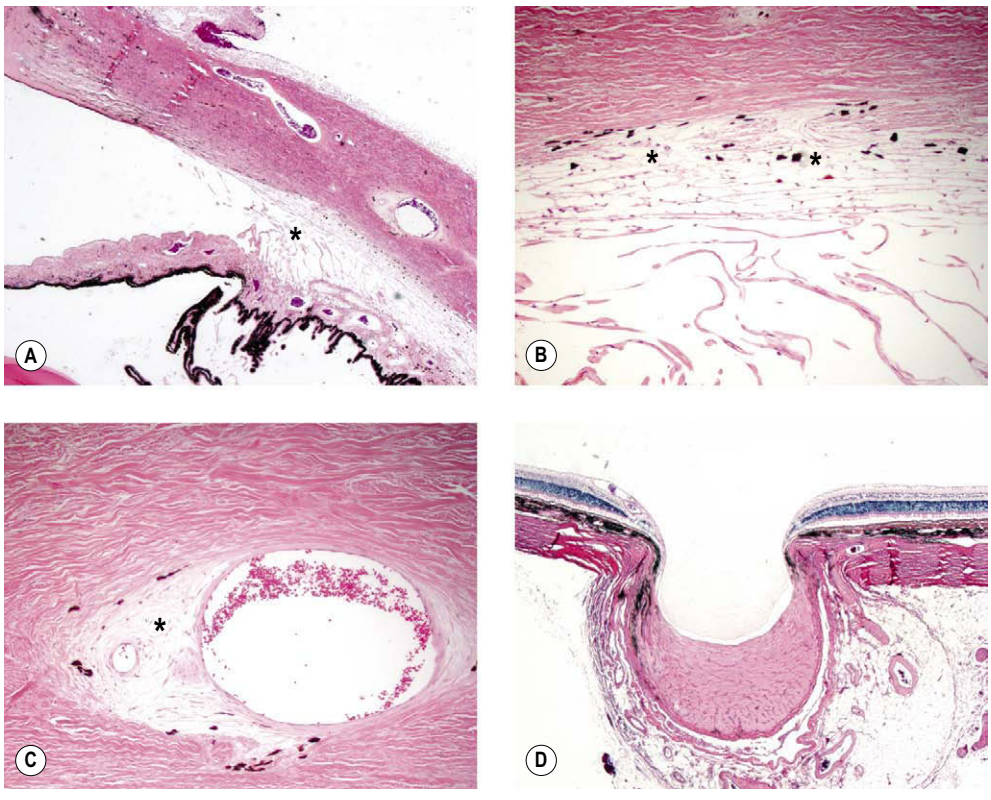


Figure 13.26 Open-angle glaucoma in cats. (A) Low magnification photomicrograph of a feline eye with open angle glaucoma showing an open and normal appearing angle (*). (B) Higher magnification of the ciliary cleft from a cat eye with open angle glaucoma showing an open ciliary cleft and corneoscleral trabecular meshwork (*). (C) Photomicrograph showing a scleral vein from an affected cat eye. The subtle myxomatous thickening around the vein (*) is characteristic of open angle glaucoma and is otherwise rarely seen. (D) Photomicrograph of a deep optic nerve cup in feline open angle glaucoma.

Descemet membrane (Haab striae). Cupping of the optic nerve occurs early but is reversible with effective treatment
- Glaucoma is seen in infants and children in association with a number of developmental or congenital abnormalities, including aniridia, Axenfeld anomaly, Rieger syndrome, Peters anomaly, and Marfan syndrome.

THE EQUINE GLAUCOMAS

As previously stated, equine glaucoma is probably under-recognized in clinical practice and under-represented in submissions to ocular pathology laboratories.

There are only 51 cases of equine glaucoma in the COPLOW collection.

- 19 also have equine recurrent uveitis
- 11 are diagnosed simply as chronic glaucoma
- 7 have uveitis other than ERU
- 3 are less than 1-year-old and have an anterior segment dysplasia or early life trauma
- 4 have trauma as an adult
- 3 have lens luxation
- 2 are listed as open angle glaucoma
- 2 have concurrent neoplasia

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